OL. XLII ISSUED IN ALTERNATE MONTHS No. 175

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UNIVERSITY OF MICHIGAN
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MEDICAL

The British Journal of Surgery

LISTER

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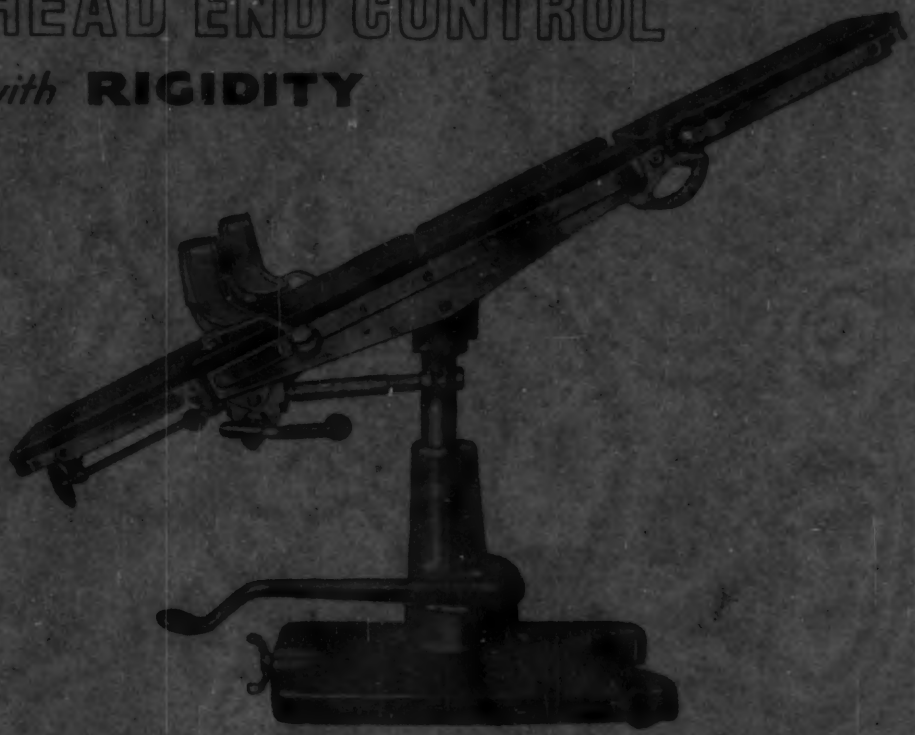

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The British Journal of Surgery

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In this system the name of the author and the date of the publication are given in the text; the list of authors quoted is put at the end of the article in alphabetical order. Each reference in the list should give, in order, the author's name, initials, the year of publication (in brackets), the full title of the paper,* the name of the journal, the volume (in heavy type arabic numerals), and the number of the first page of the paper. If the author cited has written more than one paper in the year, each should be distinguished by the letters a, b, and c, etc. For books, the place of publication should be stated and the publisher's name. The names of collaborating authors should be given in full on the first occasion, but in later citations the words "and others" should follow the first name.

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* As an economy at the present time, the title of the paper may be omitted.

THE
BRITISH JOURNAL OF SURGERY

VOL. XLII MARCH, 1955 No. 175

INVESTIGATIONS INTO THYMIC DISEASE AND TUMOUR FORMATION*

BY GEOFFREY KEYNES, LONDON

THE name of Cecil Joll has already been commemorated by two previous lecturers—Frank Lahey, of Boston, whose death we have but recently lamented, and Sir Thomas Dunhill, happily still with us. Both these men, like Joll himself, were among the most distinguished thyroid surgeons of the Anglo-Saxon world, and they naturally talked of the surgery of the thyroid gland which had occupied so large a part of their professional lives. It might be expected that in delivering the Cecil Joll lecture for 1953 I should attempt to do the same, having known Joll well; but it must be admitted that our most frequent meeting place was not the operating theatre or the consulting room—it was the foyer at Covent Garden or wherever the Russian ballet companies happened to be performing. Moreover, most of what I know about thyroid surgery I learnt from Dunhill, so that I should not be able to add much to what he has already said on this subject, of which he is the acknowledged master in this country.

I do not, however, propose to stray very far from the region of the thyroid gland. I shall go just a little farther down the morphological ladder and talk of an allied organ—called the thymus gland, though until recently there seemed to be little justification for implying by the term 'gland' that it produced an internal secretion in any way comparable to that of its neighbour, the thyroid.

Twenty-five years ago the late George Scott Williamson and Dr. Innes Pearce were trying to prove that there was a functional and anatomical continuity linking the two organs, but this doctrine was afterwards abandoned, and it seems that anatomical proximity is all that can be claimed. It would be rash to assert that the muscular asthenia sometimes seen with an overacting thyroid is closely related to the peculiar form of weakness known as myasthenia gravis, for which the thymus gland is now suspected to be responsible; but there are reasons for thinking that the two conditions are analogous, and there has occasionally been confusion between them, heightened by the claim that thyrotoxic asthenia has been known to respond to treatment with the drug neostigmin—a response which is ordinarily regarded as virtually diagnostic of myasthenia gravis. It has also been suggested that the clinical association of thyrotoxicosis and myasthenia gravis in the same patient occurs slightly more frequently than can be attributed entirely to chance. There are, however, too few examples of this to give them any real statistical significance.

It so happened that the start of my own interest in the surgical treatment of myasthenia gravis by thymectomy was due to a rather fortuitous circumstance connected with the thyroid. In February, 1942, a woman of 31 was in the National Hospital, Queen Square, with severe and progressive myasthenia gravis. It was judged by the physicians in charge that she would die unless something drastic could be done. It happened that in 1941 Blalock, of Baltimore, had reported a small number of thymectomies with fairly favourable results, and on the strength of this I was asked to do a thymectomy, which had never before been done in Great Britain for myasthenia gravis. The physicians' choice of operator fell upon me partly because I happened to have operated on this patient for mild thyrotoxicosis twelve years before. I was no doubt credited with a sort of proprietary interest, added to the fact that she still had an enlarged thyroid gland and mild signs of thyrotoxicosis—which was not, perhaps, a very strong recommendation for employing the same surgeon again. However, the operation was done, with the help of J. E. Piercy, at New End Hospital, both thyroid and thymus being attacked; the patient survived, and the myasthenia gravis was arrested and ultimately abolished. She was employed as a land-girl for many years after her recovery.

Encouraged by this initial success, we proceeded to extirpate further thymus glands from myasthenic patients at New End Hospital, at St. Bartholomew's, and at the National Hospital, Queen Square, and in due course the operation of thymectomy became well established as a recognized form of treatment for myasthenia gravis. The general problem of the thymus gland, its relation to myasthenia, and the results of thymectomy I discussed in a Hunterian Lecture given in this College on June 13, 1945 (Keynes, 1946), and a number of other communications have subsequently been made elsewhere. In this lecture attention will be directed to one special and difficult aspect of the problem, namely the thymic tumours, or thymomata, that are found in patients with myasthenia gravis, and sometimes also in patients who have no symptoms of disease whatever.

* The Cecil Joll Lecture delivered at the Royal College of Surgeons of England, November, 1953.

When we began the clinical study of the surgical treatment of myasthenia gravis singularly little was known or recorded about the incidence of these tumours. The bare fact that thymomata did occur in myasthenic patients had been known for many years, and several attempts had been made to remove them. The first observation seems to have been made by Weigert in 1901, but this was only the post-mortem discovery of a thymic tumour in a myasthenic patient. By the year 1917 there were published records of 10 thymic tumours discovered post-mortem (Bell). By 1932 the number had risen to 166 (Crosby), and many more have been reported since. The first recorded successful removal of a thymoma from a myasthenic patient was done by Blalock, of Baltimore, in 1936, using a transsternal approach (Blalock and others, 1939). This led to the general application of thymectomy in the treatment of myasthenia gravis, again initiated by Blalock, who reported in 1944 on the results of 20 operations, though only 2 of these had revealed the presence of a tumour. When we began our own series of operations in 1942 there was little or no information to be had concerning the natural history, clinical diagnosis, radiology, or treatment of thymic tumours, of which *Fig.* 539 is a typical example, and it is not surprising, therefore, that at first we only discovered them by stumbling on them at operations. This happened at the second operation in the series, the patient, a woman of 24, dying on the third post-operative day. It happened again at the fourth in the series, when we found a small tumour in a patient who survived for many years. The third occasion was the thirteenth operation, on a woman of 42, who died on the second post-operative day. Two more (the twenty-second and thirty-seventh operations) were discovered on the operating table without previous diagnosis, but thereafter we began to appreciate the possibilities of radiological diagnosis before operation, and for the last ten years (since 1944) only a few tumours have come as operational surprises. The importance of pre-operative diagnosis of tumours was impressed upon us by the post-operative results.

FIG. 539.—Tumour of right lobe of thymus (No. 6). Weight, 40·5 g. (× ¼.)

THYMIC TUMOURS WITH MYASTHENIA GRAVIS
(April, 1942–January, 1948)

Died after operation	3
Died in less than 2 years	5
Died with recurrence at 7 years	1
Probably dead	1
Alive and well at 6 years	1
Total	11

Of the first 11 tumour patients operated on, that is between April, 1942, and January, 1948, only 3 survived for more than two years, and only 1 is known to be alive at the present time. Three of the eleven died post-operative deaths. This is in striking contrast to the general results of thymectomy when there is no tumour. Among these the post-operative mortality is 4 per cent, and 65 per cent of the survivors are apparently cured or very nearly so. It also became more and more plain that tumour formation was to be expected in a considerable proportion of patients with myasthenia gravis.

PATIENTS WITH MYASTHENIA GRAVIS
(1942–1953)

No tumours	219
With tumours	41
Total	260

Incidence of tumours 15·4 per cent

Of 260 patients who have come under my notice, 41 have had thymomata, an incidence of 15·4 per cent, so that the problem of the tumours is clearly an important one in relation to thymic surgery in general. Also the bad results of primary surgery demanded a fresh approach to the problem of treatment. In assessing the results of simple thymectomy we have, therefore, excluded the tumours, these patients for some years having been treated differently from those without tumours, as I have emphasized in everything that I have hitherto published on thymic surgery.

The present study of the thymic tumours is an attempt to focus attention on this particular problem by using for the first time an adequate accumulation of material. Thymic tumours used to be thought exceedingly uncommon, but I am now able to review a series of 51, 41 having come under my own observation and 10 others having been kindly contributed by four other surgeons, namely Dickson Wright (1), Norman Barrett (4), A. L. d'Abreu (3), and Ian Hill (2). From this survey it may be possible to draw conclusions of value concerning their natural history, pathology, diagnosis, and treatment. It has not been possible to learn much about them from the sporadic accounts of single examples or of small numbers that have been published hitherto. (*Table I.*)

The whole subject has for long been in confusion because of the variety of tumours that may arise in

Table I.—THYMIC TUMOURS. DETAILS OF 51 CASES

Table I.—THYMIC TUMOURS. DETAILS OF 51 CASES

No.	Serial No.	Surgeon	Sex	Age	Duration	Severity	Radiology	Deep X-ray Therapy	Operation	Result
1	2	G. L. K.	F.	24	Short, 6 mth.	+ + general	—	—	April 4, 1942, removed	Died April 7, 1942
2	4	G. L. K.	M.	34	3 yr.	+ + general	—	For recurrence, 1948	May 9, 1942, removed	Partial recovery. Recurrence 6 yr. Died Nov. 5, 1949
3	13	G. L. K.	F.	42	Short, 10 wk.	+ + general	—	—	Nov. 9, 1942, not removed	Died Nov. 11, 1942
4	22	G. L. K.	F.	35	Short, 3 mth.	+ + general	—	—	Aug. 21, 1942, removed	Recovery. Relapse. Died Nov. 24, 1943. P.M., nil
5	37	G. L. K.	M.	34	Short, 8 wk.	+ + + general	—	—	Nov. 18, 1944, removed	Recovery. Relapse. Died Feb. 13, 1945. P.M., nil
6	47	G. L. K.	F.	47	2 yr.	+ + general	Seen	—	June 4, 1945, removed	Recovery. Relapse. Died March, 1947
7	53	G. L. K.	F.	58	Short, 15 mth.	+ + + general	Seen	—	Oct. 11, 1945, removed	Recovery. Relapse. Died May, 15, 1947
8	75	G. L. K.	M.	31	Short, 6 mth.	+ + + general	Seen	—	Oct. 30, 1946, removed very large (160 g.)	Recovery. Relapse. Died Nov. 25, 1946. P.M., nil
9	81	G. L. K.	M.	50	Short, 5 mth.	+ general	Seen	Post-operative, June, 1947	Jan. 30, 1947, removed	Recovery. Relapse. Maintained on TEPP to November, 1948
10	98	G. L. K.	F.	38	2 yr.	+ + general	Seen	July 17 to Aug. 29, 1947	Sept. 3, 1947, removed	Recovery. Relapse. Recovery July, 1953, slight ptosis only
11	107	G. L. K.	M.	30	Short, 6 mth.	+ + general	Not seen until after operation	—	Jan. 9, 1948, not removed	Died Jan. 14, 1948, bronchopneumonia
12	113	G. L. K.	F.	41	Long, 11 yr.	+ mainly bulbar	Not seen	Post-operative, May, 1948	April 14, 1948, removed	Recovery. Relapsed December, 1952. Died Dec. 16, 1952
13	115	G. L. K.	M.	39	Short, 14 wk.	+ mainly bulbar	Not seen	Post-operative, May, 1948	April 21, 1948, removed	Recovery. Improved
14	118	G. L. K.	F.	35	Short, 1 yr.	+ general	Not seen	—	May 7, 1948, removed	Recovery. Improved. Relapse August, 1950
15	128	G. L. K.	M.	52	Short, 3 mth.	+ + general	Seen	June to August, 1948	Sept. 9, 1948, not removed	Improved. Relapse. Died March 3, 1950
16	137	G. L. K.	F.	32	Long, 5 yr., with 3 yr. remission	+ + mainly bulbar	Seen	August, 1948	Nov. 10, 1948, removed	Recovery. Quite well
17	139	G. L. K.	M.	55	Long 3½ yr.	+ + general	Not seen until after operation	February 1949, post-operative	Jan. 14, 1949, removed	Recovery. Almost well
18	181	G. L. K.	F.	66	1½ yr.	+ + general	Not seen	July 1950, post-operative	June 20, 1950, removed	Recovery. Improved. Relapsed. Again improved
19	184	G. L. K.	M.	58	Short, 7 mth.	+ + general	Seen	April 3, 1950	July 12, 1950, removed	Recovery. Relapse May, 1953. Died July 26, 1953
20	187	G. L. K.	F.	40	Short, 1 yr.	+ general	Seen	April, 1950	Aug. 21, 1950, removed	Recovery. Quite well
21	190	G. L. K.	M.	37	Short, 4 mth.	+ + general	Seen	February, 1949	May 18, 1949, removed	Recovery. Quite well
22	216	G. L. K.	M.	42	2 yr.	+ + general	Seen	December, 1950	July 4, 1951, removed	Recovery. Relapsed. Died Feb. 13, 1952
23	217	G. L. K.	F.	53	2 yr.	+ mainly bulbar	Seen	October, 1950	July 18, 1951, removed	Recovery. Much improved
24	220	G. L. K.	M.	47	Short, 2 mth.	+ + general	Not seen	November, 1951, post-operative	Aug. 24, 1951, not removed	Recovery. Quite well
25	224	G. L. K.	M.	48	1½ yr.	+ + general	Seen	April to June, 1951	Aug. 24, 1952, removed with great difficulty	Recovery. Improved
26	233	G. L. K.	F.	57	Long, 12 yr.	+ + general	Seen	December, 1951	Feb. 13, 1952, removed	Recovery. Not improved
27	234	G. L. K.	F.	47	Short, 9 mth.	+	Seen in tomogram	October to December, 1951	Feb. 20, 1952, removed	Recovery. Improved
28	240	G. L. K.	M.	31	Short, 3 mth.	+ + general	Seen in tomogram	January to February, 1952	March 19, 1952, removed	Recovery. Quite well
29	—	G. L. K.	M.	69	Short, 3 mth.	+ + + general	Seen, with calcification	December, 1950	—	Died Dec. 30, 1950
30	—	G. L. K.	F.	50	2 yr.	+	Seen	November, 1948	—	Improved
31	—	G. L. K.	M.	27	Short, 9 mth.	+ bulbar	Seen	April to June, 1952	—	Died Oct. 13, 1952
32	—	G. L. K.	F.	54	5 yr.	+ + general	Seen	June to July, 1950	—	Some improvement. Relapse. Died Jan. 5, 1951
33	—	G. L. K.	F.	38	Short, 3 mth.	+ + general	Seen	May, 1945 —	—	Died May, 1945
34	—	G. L. K.	F.	54	Long, 7 yr.	+ general	Seen, very large with calcification		Feb. 18, 1946, not removed	Died under anæsthetic

Continued overleaf

Table I.—THYMIC TUMOURS. DETAILS OF 51 CASES—*continued*

No.	Serial No.	Surgeon	Sex	Age	Duration	Severity	Radiology	Deep X-ray Therapy	Operation	Result
35	—	G. L. K.	F.	37	Short, 3 mth.	+ bulbar	Seen	June to July, 1946	—	Quite well
36	255	G. L. K.	F.	49	1½ yr.	++ general	Seen	May to June, 1953	Oct. 22, 1953, removed	Died Oct. 23, 1953
37	256	G. L. K.	F.	42	1 yr.	++ general	Seen	June, 1953	Nov. 26, 1953, removed	Recovery. Not improved
38	—	G. L. K.	M.	39	3 yr.	++ general	Seen	October to November, 1949	—	Unchanged. Died April 27, 1952
39	—	G. L. K.	F.	55	Long, 7 yr.	++ general	Seen	June, 1953	—	Almost well
40	—	G. L. K.	F.	49	1½ yr.	++ general	Seen	June, 1953	—	Much improved
41	—	G. L. K.	F.	60	Short, 8 mth.	++ general	—	—	—	Died Aug. 28, 1950, soon after first seen. P.M., invasive tumour
42	—	I. H.	M.	54	Long, 13 yr.	+	Seen	—	Jan. 9, 1953, removed	Unchanged
43	—	I. H.	M.	40	Short	—		1953	—	Died
44	—	A. L. d'A.	F.	36	Short, 4 mth.	++ general	—	1950 and post-operative	March 13, 1952. Removed with part of lung	Recovery. Quite well
45	—	A. L. d'A.	F.	57	Short, 7 mth.	General	Not seen	—	Dec. 19, 1952, removed	Died post-operative
46	—	A. L. d'A.	F.	54	1½ yr.	—	Seen	1951	July 20, 1951, partly removed	Died July 24, 1951
47	—	N. B.	F.	30	Short, 4 mth.	++ general	Not seen	—	Jan. 29, 1952, removed	Recovery. Improved. Relapsed. Died June 22, 1952. P.M., nil
48	—	N. B.	F.	39	Short, 3 mth.	Bulbar	?	—	Oct. 14, 1952, removed	Recovery. Improved
49	—	N. B.	M.	34	2 yr.	Mainly bulbar	Seen	—	Feb. 25, 1952, removed	Recovery. Improved. Relapsed. Improved. At work as clerk
50	—	N. B.	M.	50	Short, 7 mth.	++ general	—	—	April 25, 1946, removed	Died April 26, 1946
51	—	D. W.	M.	35	1 yr.	+ general	—	—	July, 1946, removed	Recovery. Quite well

the mediastinum, the uncertainty as to which of them have really arisen from the thymus gland, and the difficulty experienced by pathologists in classifying the true thymomas or even in settling their correct nomenclature. All the earlier accounts of mediastinal tumours included sarcomas, teratomas, reticuloses, and even secondary growths, together with true thymic new growths and simple thymic hyperplasia, so that a composite and misleading impression resulted. Pathologists have never really made up their minds whether to call the true thymomas innocent or malignant and the very name of *lympho-epithelioma* that they have commonly applied to them betrays their uncertainty. Even when using this name, in which the term *epithelioma* implies malignancy, they have often pronounced them benign. A little light may be shed on those vexed questions by concentrating on a comparatively long series of examples, all of which were associated with symptoms of myasthenia gravis.

To illustrate further the difficulty of the subject I must record the answer I received from a thoracic surgeon, Sir Russell Brock, when I asked him how many thymic tumours he had encountered which were *not* associated with myasthenia gravis. He furnished me with the following *list* :—

Teratoblastoma	3
Teratoma	7
Epidermoid cyst	8
Lymphatic or 'spring-water cyst'	3
Hodgkin's disease	1
'Thymoma'	3
	25

Brock is convinced that practically all of these were indeed arising in the thymus gland, particularly the teratomata and epidermoid cysts, and his opinion, based on ocular demonstration, obviously cannot be passed over, although it is not altogether in agreement with current opinion.

Fig. 540 shows an example of an irrelevant tumour in a thymus which I removed from a myasthenic patient. It was a large firm white mass in one lobe of the gland, but it proved in section to be a simple fibroma.

The natural history of thymomas associated with myasthenia gravis may first be illustrated by examining the *sex* and *age* incidence, the severity of the disease, and the clinical course.

Sex Incidence.—Male 22 (43 per cent), female 29 (57 per cent), with thymoma. This is a much higher proportion of males than was found in myasthenia without tumours : Male 66 (31 per cent), female 145 (69 per cent).

Age Incidence.—The age incidence in successive decades is strikingly different (*Table II*).

Thus of patients with tumours none was under 20, and only 4 per cent were under 30, while the biggest number was in the decade 30–39.

These figures are quite different from those obtained for patients without tumours. Of these, 49 per cent were under 30, over 14 per cent being in infants, children, and adolescents, an age group which provided no tumours at all. The largest number were in the decade 20–29. In the decades 40–49, 50–59, and over 60 the proportion of tumours rises steeply. It is clearly seen, therefore, that tumour

formation is a disease of the older victims of myasthenia gravis.

I suspect that thymomas may be commoner than appears in the oldest patients of 60 and upwards. These elderly patients would not be likely to survive

FIG. 540.—Simple fibroma in left lobe of thymus. (× ⅓.)

for long, and so would not often come under the surgeons' observations. This is bound up with the next heading.

The Severity of the Disease.—This is very difficult to express in precise figures, but clinical experience shows quite conclusively that the presence of a tumour is nearly always associated with severe symptoms, which are difficult to control. The respiration is not uncommonly affected. The response of these patients to neostigmin is slow and sometimes incomplete so that suspicion should be aroused at an early stage. Usually the symptoms are generalized, but even when there is the uncommon association of a tumour with symptoms confined to the bulbar area, these restricted symptoms are of a severe type. There is, of course, no rule about this. Myasthenia gravis never obeys any rules whatever; it is erratic in its every manifestation, but it is safe to make the broad statement here given about its severity with tumours.

The Duration of the Disease.—This feature is important in the natural history. Myasthenia gravis in general shows a very wide variation in its rates of onset. Commonly it is slow, the earliest symptoms having occurred a number of years before the diagnosis is made or any treatment instituted. But investigation of thymic tumours shows that the onset of the myasthenia is usually very much more rapid. A few of the patients had histories of 3, 5, or 7 years, and one was as long as 12 years, but 40 patients out of 51 had a history of only 2 years or less, and 26 had a history of 12 months or under. A duration of only three months was common, and in one it was only one month. *Rapidity of onset* is, in fact, a conspicuous feature of the myasthenia due to a thymoma.

In this connexion it is of interest to have an account of the onset of the disease in the actual words of a young man of 31 (No. 28):—

"On August 19, 1951, I took part in a cricket match which seemed to exhaust me completely. In particular, I recollect having had the greatest difficulty in recovering my breath after a spell of bowling or batting. For a period of about a fortnight after this game I suffered considerable stiffness and pain throughout my body. I was not unduly concerned by these discomforts as they in no way hindered me in my normal daily round: rather did I regard them as the natural outcome of not having taken any strenuous exercise for some time.

"At about the beginning of September I noticed that my right arm seemed to hang somewhat heavily and I had trouble in reaching with my right hand to my hip trouser pocket. During the following ten days or so the loss of power in this arm became more evident. I found, for example, that sawing a piece of wood necessitated my holding the saw with both hands. Similarly, when using a screwdriver, a paint brush, or even a table knife, I could not exert sufficient pressure to operate them successfully.

"Towards the end of the third week of September my eyes started to bother me, particularly when I was at the office. I began to have double vision, and on looking up from my desk to a more distant object I saw two images. My eyes watered a good deal.

"From this time onwards my condition deteriorated rather rapidly and symptoms followed each other more quickly. On September 27 I first noticed the nasal-sounding twang in my voice which developed after I had been speaking for a short period. My voice recovered its normal tone after a rest, but weakened again on further talking, until whatever I was trying to say became almost

Table II.—AGE INCIDENCE

	Decades						
	0–9	10 19	20–29	30–39	40–49	50–59	60
Tumours	0	0	2 (4·3 per cent)	19 (39·6 per cent)	11 (23 per cent)	13 (27·3 per cent)	3 (6·2 per cent)
No tumours	4 (2 per cent)	26 (12·3 per cent)	74 (34·9 per cent)	67 (31·6 per cent)	31 (14·6 per cent)	8 (3·6 per cent)	2 (1 per cent)

unintelligible. During the time I was speaking my eyelids drooped involuntarily, but recovered after a rest.

"In the evening during dinner, I quite suddenly spluttered and choked and discovered that food was finding its way down my nose. The following day, September 28, I remained in bed and I remember that I had no further difficulty then in swallowing food or drink, and the tone of my voice seemed normal.

"The next morning, I had difficulty in raising myself up in bed; the upper part of my body seemed

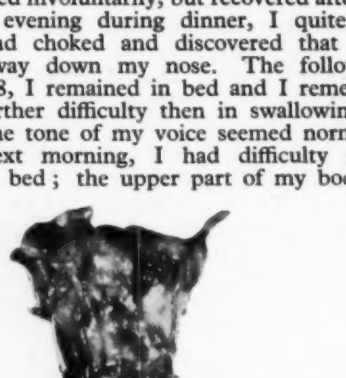

FIG. 541.—Tumour occupying greater part of thymus (No. 28). (× ¼.)

exceedingly heavy. The double vision was quite pronounced, but I found some relief in wearing an eye-shield over one eye. In the evening my doctor brought in a polio specialist to examine me. I remember that at this stage I could not raise my head from my pillow; my legs, however, were entirely free from weakness. Later the same night a lumbar puncture was performed and I commenced medicinal treatment for suspected polio.

"During the next ten days, which I spent at home, I could not swallow solids or liquids without ejecting some down my nose. At night my breathing became very laboured from time to time and my chest sounded bubbly. The entire upper half of my body was affected, my head lolled on my shoulder, and my jaw used to drop open. I could not voluntarily close my eyes, nor smile.

"On October 10 I was admitted to hospital, where my condition was immediately recognized. After a trial period I was started on regular doses of 180 mg. prostigmin daily. During my stay in hospital my jaw muscles and hands weakened considerably, and in spite of prostigmin failed to function properly.

"I left hospital on November 7, but soon discovered I required larger doses of prostigmin to keep going. I also noticed that I could not always rely on the effectiveness of a dose when taken. Of a morning I often required 45 mg. to enable me to sit up in bed.

"By the middle of November my legs were affected. I was unable to dress or undress without assistance. I could not sit in an armchair and be sure that I could raise myself from it when necessary. Mounting stairs became difficult. At this time I was taking about 300 mg. daily."

Here we have a very complete picture of extremely severe myasthenia gravis developing relentlessly and rapidly in the course of less than three months. The dose of neostigmin was continually increased, but was not effective when given, and the patient's condition was pitiable. Fortunately for him, this young man was not one of the earlier ones in the series, and he is now quite well, three years after the removal of an extensive lobulated tumour (*Fig.* 541).

As already indicated, there have been some remarkable exceptions to this general rule of rapid onset. One patient, a woman of 57 (No. 26), had had symptoms of myasthenia for twelve years. Three years after the onset she was seen in the New End clinic, but was dismissed because the symptoms were so mild. Nine years later she returned with generalized myasthenia which had recently become severe, and a small tumour was diagnosed by radiography. It seems improbable that the tumour was present when she was first seen. It appears to have formed after a long interval in a mildly myasthenic patient—a warning that thymectomy should not necessarily be withheld because the symptoms are mild. Early operation may forestall more serious developments.

Another woman of 54 (No. 34) had had mild generalized myasthenia for seven years, and had gradually developed dyspnœa, though the myasthenia had lessened. She was found to have an enormous mediastinal tumour with many areas of calcification (*see Fig.* 555). The tumour was explored, but proved to be not removable. The patient developed acute myasthenia on the operating table with paralysis of the respiratory muscles. She was kept alive for some hours with oxygen, atropine, and neostigmin. This patient had reached the extremity of disease before any thymic tumour was suspected, though it must have been present for many years. Usually a small tumour is responsible for severe symptoms—here it was the other way round.

Treatment.—As already shown, treatment of the tumour by primary operation proved to be exceedingly unsatisfactory, at any rate in my hands. Exceptions can, of course, be recorded. Dickson Wright has removed only one thymic tumour. This patient was a man of 35 (No. 51) who had had symptoms of myasthenia for a year. Six years later he is perfectly well, felling trees. Usually, however, a more cautious approach is to be recommended. Firstly, the operative risk is increased by the presence of a tumour. It often becomes closely adherent to the mediastinal pleura on one or both sides. The adherent pleura is greatly thickened; sometimes it can be peeled off the surface of the tumour, but more often this is impossible. The pleura becomes torn or a portion has to be excised and it may be impossible to close the opening. If this happens on both sides there is a serious risk of post-operative collapse of the lungs, which is very likely to be fatal in a myasthenic patient. Also the tumour may become adherent to neighbouring structures. It can sometimes be separated cleanly from the aorta, but if the left innominate vein is adherent or surrounded, this may have to be excised. Again the lung may be adherent or infiltrated, and in one patient (No. 44) under the care of A. L. d'Abreu part of a lung had to be removed with the greater part of the tumour. If the tumour is surrounding or infiltrating the root of a lung, complete removal is likely to be impossible. Even if all

these hazards have been absent or overcome, so that complete removal of the tumour with the rest of the thymus gland has been accomplished, the patient may make a good recovery from the operation, but yet die soon afterwards from a relapse into a state of acute myasthenia. This happened in five of my patients in succession (Nos. 4–8). All made good recoveries from their operations, one (No. 8) having been rid of an enormous tumour weighing 160 g. which necessitated widely opening the pleura on both sides. Some of them completely lost their symptoms for a time, and relapsed after intervals varying from a few weeks to a few months. The myasthenia became irreversible, that is to say neostigmin became quite ineffectual, and death followed from respiratory paralysis. In one young man, a farmer aged 34 (No. 5), a massive tumour occupied one lobe of the thymus (*Fig.* 542). He made a good recovery and lost all his symptoms for a time, but relapsed a few weeks later and died with irreversible myasthenia. In this man and in two others whose bodies were subjected to a post-mortem examination nothing whatever was found to account for this outcome. There was no residual tumour or thymic tissue and no metastases or accessory growths. As to how the abnormal thymus gland or thymoma produces on the neuromuscular mechanism the effect seen clinically as myasthenia gravis, it can now only be said that it is believed to discharge an abnormal secretion into the circulation which somehow inhibits the production of acetylcholine, the deficiency resulting in muscular

FIG. 542.—Tumour in left lobe of thymus (No. 5; specimen in R.C.S. museum). Weight, 66 g. (× ½.)

paralysis. Professor Andrew Wilson, of Liverpool University, working with material derived chiefly from my patients, has recently published important laboratory evidence on this point (Wilson, 1952; Wilson, Obrist, and Wilson, 1953). He has succeeded in preparing a potent extract from myasthenic glands which will have a specific action on a muscle-nerve preparation, the contractions being consistently reduced. A small animal can even be rendered helpless. It appears clinically that in certain circumstances there is a cumulative effect ending in complete arrest of the normal mechanism with respiratory paralysis. This may happen sometimes in a patient without a tumour, but in my experience it is particularly liable to happen in

FIG. 543.—Thymic tumour, cystic, after irradiation. Post-mortem specimen (No. 32). (× ⅛.)

patients with tumours even though they have been completely removed. An alternative treatment therefore had to be tried.

Radiotherapy.—In 1947, only six years ago, very little was known about the reaction of thymic tumours to high-voltage X-ray therapy. I therefore enlisted the help of the radiotherapy department at St. Bartholomew's under I. G. Williams, and for five years every thymic tumour diagnosed before operation has been treated by means of the million-volt machine, and a few patients in whom the diagnosis was missed have been treated very soon after operation. Up to the present time 26 of my patients have been treated in this way, 21 of whom have subsequently had an operation performed. In one (No. 15) the tumour was not removable, and the patient died eighteen months later.

THYMOMAS TREATED WITH DEEP X-RAY THERAPY FOLLOWED BY OPERATION (1948–1953)

Died later	4
No improvement	1
Improved but relapsed	3
Much improved	8
Quite well up to 5 years	4
Total	20

Of the remaining 20 patients, 4 have died, 1 was no better, 3 improved at first but afterwards relapsed, 8 have considerably improved, and 4 are quite well and symptomless.

This is a very different result from that obtained earlier in the series with primary operation. Fifteen

of the eighteen patients are alive and 4 are perfectly well. One other has been recently treated with deep X-ray therapy and operation will be considered later. The technique of the treatment, which has been described by I. G. Williams (1952), is not easy and demands very careful management of the patient's symptoms. Not uncommonly the myasthenic symptoms become accentuated at some stage of the

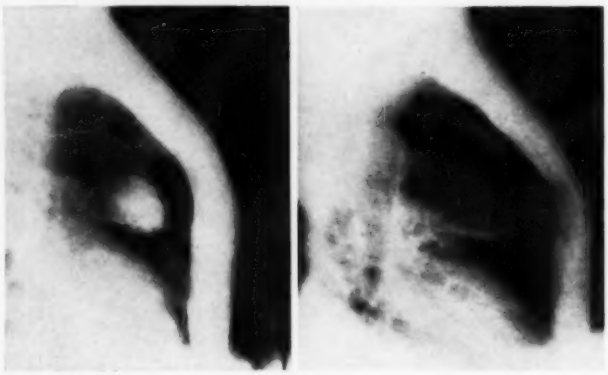

FIG. 544.—X-ray films of thymic tumour before and after deep X-ray therapy (No. 15).

treatment, which may have to be interrupted for a longer or a shorter period. Great accuracy of exposure to the X-ray beam is desirable to avoid injury to the lungs, so that precise localization of the tumour by preliminary radiology is essential. Tomography may be of great assistance. The total dosage, up to 4000 r, may have to be spread over a period of four weeks or sometimes a good deal longer.

During the course of the X-ray treatment the tumour, as demonstrated by radiology, can be seen to shrink and sometimes to become less opaque. Sometimes the tumour cells seem to disappear with the treatment, as in the example shown. The patient (No. 32) improved somewhat, but never came to operation and died five months afterwards. Post mortem (*Fig.* 543) she was found to have a small cystic tumour, showing no identifiable cells, but with cholesterin crystals and calcification. The tumour cells, however, seldom disappear completely; usually viable cells remain, and I am sure that surgical removal should be done if there are no contra-indications and if it is possible. *Fig.* 544 is an example of a tumour which became much less opaque to X rays after six weeks' radiotherapy. At operation afterwards the tumour proved to be not removable and a biopsy specimen showed the presence of viable tumour cells. The patient, a man of 52 (No. 15), improved somewhat at first, but died within two years of his first attendance at hospital. Another patient (No. 16) showed a similar change in the tumour after irradiation, the main mass becoming smaller and less opaque. At operation a large lobulated tumour was removed with difficulty, yet the patient is symptomless and quite well four and a half years later. Williams has emphasized that, if it were attempted to destroy completely the epithelial cells of the tumours, the X-ray dose would have to be much increased, with greater danger to the patient. In 2 patients who suffered pulmonary or cardiac complications no operation has been done. Both have nevertheless improved, one being quite free from myasthenia six years after the treatment, so that X-ray treatment alone is worth trying even though operation is not possible.*

The operation is not, on the whole, made more difficult by X-ray treatment; in fact, shrinkage of the tumour may make it a little easier. Sometimes,

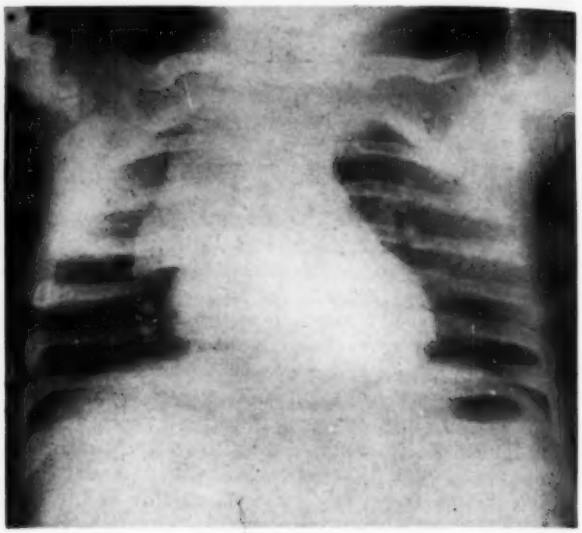

FIG. 545.—'Sail shadow' in radiograph of normal infant (negative view). (*By courtesy of the Nuffield Institute, Oxford.*)

however, the usual fibrosis surrounding a tumour is accentuated, and I recall one instance (No. 25) where I was confronted with a fibrotic mass occupying the upper half of the mediastinum which had obliterated most of the left innominate vein. An American visitor behind me was heard to remark in a loud whisper, "He can't possibly remove it!". This opinion had its natural effect; there were some bad moments when a large, though unidentifiable hole had been torn in the side of the right innominate vein but the mass was successfully removed with the left innominate vein, and the patient is fairly well two years later.

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* This point may be further emphasized by the history of another patient, a man of 47 (No. 24). His history was short. He was admitted to the National Hospital, Queen Square, two months after the onset of ptosis, slurred speech, and difficulty in chewing and swallowing. Symptoms progressed rapidly and became general. No tumour was seen in X-ray films, but at operation on August 24, 1951, a tumour was found on the left side of the aorta. No attempt was made to remove the tumour and the chest was closed. A course of deep X-ray therapy at St. Bartholomew's Hospital was given during September–November, 1951, but this was not quite completed owing to a series of severe myasthenic crises. In January, 1952, he was taking 20–25 tablets (15 mg.) of neostigmin daily. By August, 1952, he was at work taking 15–20 tablets. In December the dose was reduced to 5 tablets; in June, 1953, to 3 tablets. In November he ceased to take them altogether. In May, 1954, he was still not taking any drug at all and able to carry a load of 2 cwt. up a flight of stairs. Recovery has, therefore, been complete, though gradual, after X-ray therapy only.

Radiology.—I have already referred to our initial failure to diagnose the thymic tumours before operation. This happened in the first five tumour patients. The sixth, in May, 1945, was identified in the X-ray film, and since then all patients have been carefully examined by radiology beforehand. Gradually we have educated ourselves to know what to look for and where to look for it, but our progress was not, perhaps, as fast as it might have been because we had to educate the radiologists as well and carry them along with us. I do not blame them, because their lack of experience in this field of diagnosis was, to begin with, as complete as our own. R. A. Kemp Harper, radiologist to St. Bartholomew's Hospital, will not mind if I recall that on more than one occasion he came to the operating theatre at my summons to see the actual tumour which he had not detected in the X-ray film. With the help of the radiologists only 7 tumours out of 34 since May, 1945, have not been seen before operation. Usually re-examination of the films after operation led to their detection, and now we regard it as a serious reproach if even a small tumour eludes our vigilance. Kemp Harper soon realized the importance of tomography in this connexion. This has for some years been done as a routine both at St. Bartholomew's and at New End, and on at least two occasions the tumour was seen only in the tomographs. On another occasion the tomograph located a very small tumour in the anterior mediastinum, and this was assumed to be a thymoma because the patient, a woman of 65, had severe myasthenia; but she also had Paget's disease of the breast and she died of a multiplicity of diseases. It was found post mortem that the tumour was a secondary carcinoma of the breast.

It has often been stated that the thymus gland is usually enlarged in myasthenia gravis, and I have seen many X-ray reports stating, "No enlargement of the thymus gland detected". In fact, I have never seen any X-ray evidence of a thymus gland in a myasthenic patient apart from the tumours, though I believe it is correct to say that the normal thymus may occasionally be detected in an infant as the so-called 'sail shadow' (*Fig.* 545), and I have even seen it once in a boy of 4 years (*Fig.* 546), but this is very unusual. At one time this would probably have been called 'status lymphaticus', and in fact this boy's parents were solemnly warned against allowing him to have any operation entailing an anæsthetic.

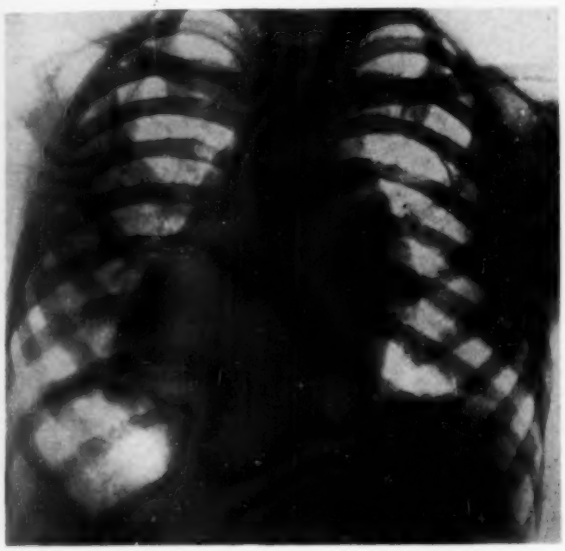

FIG. 546.—Thymic shadow in normal boy, age 4 years.

FIG. 547.—Thymic tumour, anteroposterior view, seen to left of aorta (No. 4).

When, however, a nasal operation became imperative I advised that it should be done—and it was, with perfect safety. We may assume, therefore, that no thymus gland without a neoplasm is likely to be seen in an X-ray film of an adult, but I believe that almost every tumour can be detected in films taken in the correct position and with correct exposure. The opacity of the tumours is probably due partly to the thick fibrous capsule with which most of them are invested.

Thymic tumours have been reported as sometimes occurring in abnormal situations. One intra-pulmonary tumour has been described (McBurney, Clagett, and McDonald, 1951), and another which was behind the superior vena cava (Seybold, McDonald, Clagett, and Good, 1950). I have not yet, however, encountered one that was not, at any rate mainly, in the anterior mediastinum. The most characteristic position is overlying the root of the aorta and the upper part of the pericardium. The larger tumours will be very close to the deep surface of the sternum. If the tumour is centrally placed and not wide, its shadow will be lost in that of the heart and aorta. In the example shown in *Fig.* 547, the fourth of the series, which we failed to see before operation, there is only a suggestion of a lateral projection. The greater part of the tumour is not seen.

In *Fig.* 548 the tumour is partly seen to the left of the aorta, but is seen in the lateral view (*Fig.* 549) to be large and overlying the heart. It was still very large after irradiation, but was successfully removed (*Fig.* 550), and the patient is well with only slight symptoms six years later.

The anteroposterior view of the mediastinum is, therefore, quite inconclusive if it appears to be negative. It is essential to see a film taken in the *true lateral* position, for in this view practically every tumour can be detected with certainty. If there is any doubt, it can be dispelled by a tomograph.

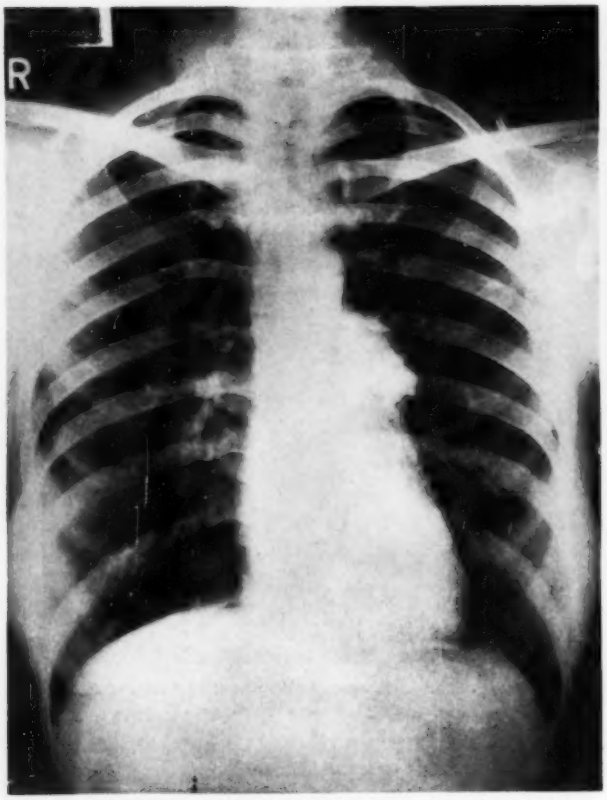

FIG. 548.—Thymic tumour, anteroposterior view, seen to left of aorta (No. 10).

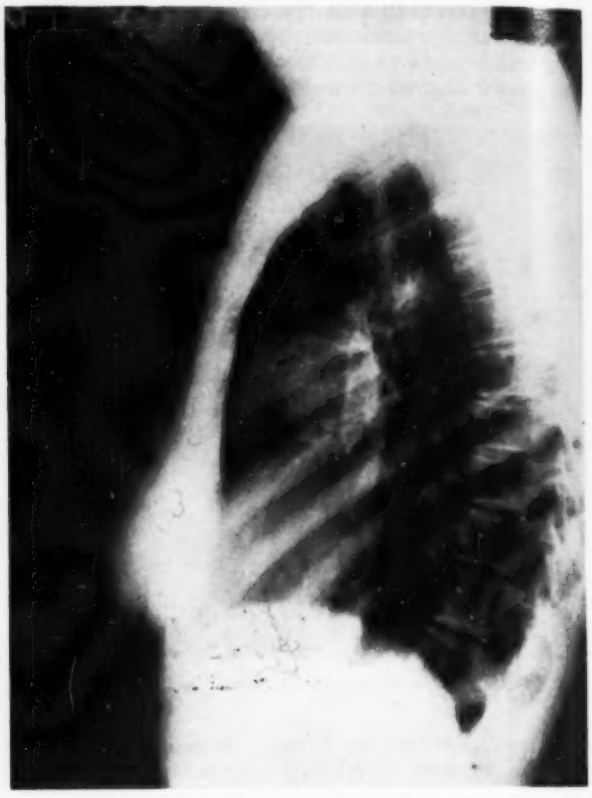

FIG. 549.—Thymic tumour, lateral view (No. 10).

FIG. 550. - Thymic tumour (No. 10). (× $\frac{1}{10}$.)

Pathology.—Any attempt to discuss the pathology of thymic tumours is entering a very difficult field. I have already referred to the great variety of tumours that are believed to arise in the thymus. Many of these, such as most of those in Brock's list, are not related in any way to myasthenia gravis and do not come into the present discussion. On the other hand, the large thymic masses that are occasionally removed from infants may serve as an introduction to the histological study of thymomas. A. L. d'Abreu has furnished a report on one of these. The infant, aged 1 year 9 months, had suffered from increasing dyspnœa since birth, with an obvious mediastinal shadow in the radiograph. A thoracotomy was done through the bed of the fifth rib and almost the whole thymus gland, weighing 57 g., was removed with relief of the symptoms. The left lobe was much larger than the right, but showed in section the structure of a thymus gland with Hassall's corpuscles, reticular cells, and thymocytes in normal proportions. Both the Hassall's corpuscles and the reticular cells are believed to be derived from epithelial cells, namely those lining the outer and inner walls of the third branchial complex, and either of these theoretically could give rise to epithelial neoplasms.

The ectodermal Hassall's corpuscles are not, however, thought to be responsible for the internal secretion producing myasthenia gravis. They are normal or reduced in the ordinary myasthenic thymus. The endodermal reticular cells, however, are very often more conspicuous than is normal,

and these large clear cells suggest by their appearance that they are the precursors of most of the tumours associated with myasthenia. It would also be

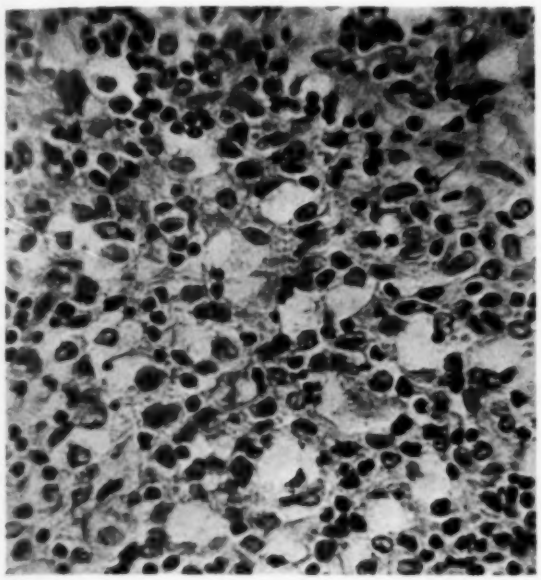

FIG. 551.—Malignant thymoma from a child, age 2, showing cytoplasmic reticulum. (*A. L. d'Abreu's patient, United Birmingham Hospitals; by courtesy of Dr. H. S. Baar.*)

logical to suppose that the proliferated mass of cells, if they are indeed identical with the active reticular cells, would produce the severe symptoms of disease so commonly associated with the tumours.

The collections of large clear cells resembling the 'germinal centres' of ordinary lymphoid tissue are common in myasthenic thymus glands, but are rarely seen in others. It is conceivable that these aggregations are the precursors of the tumour cells. A thymus from a myasthenic boy of 16 showed an irregular proliferation of epithelial cells which under high-power magnification looked very much like those in a thymoma.

Bratton (1948) has reported on the structure of 18 tumours from patients with myasthenia gravis and found that they always consisted of two types of cell —the ordinary round cell, or thymocyte, and large pale cells resembling the reticulocytes (*Figs.* 551, 552). In some one predominated, in some the other; in yet others they were more or less in equal proportions.

In *Fig.* 553, taken from the largest tumour yet investigated (No. 34), the thymocytes predominate, and the tumour was an almost solid mass of round cells.

In another fleshy-looking tumour (*Fig.* 554) the two types of cell are both conspicuous. I have examined sections of all those tumours that I have removed and can confirm Bratton's statement, but this is not the place for a detailed account of the histology. The picture is complicated by the fact that many of the tumours have been altered by X-ray therapy. In general I may say that the epithelial cells are usually predominant and that there seems to be no reason to doubt their origin from the reticular cells already mentioned. The thick fibrous capsule is always seen, and dense trabeculæ between islands of epithelial cells are usually present.

As Bratton says, the structure of all these tumours conforms to the conception of so-called 'lympho-epithelioma' of the thymus, yet in spite of the

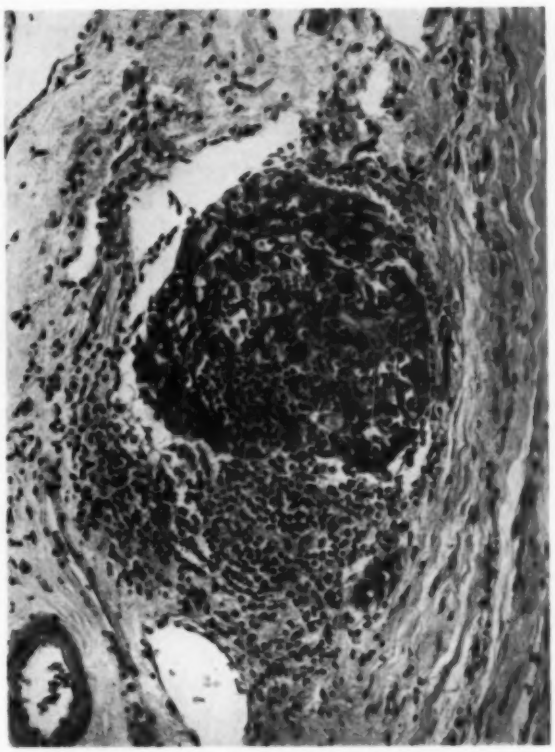

FIG. 552.—Thymoma showing cystoplasmic reticulum (No. 21). (× 150.)

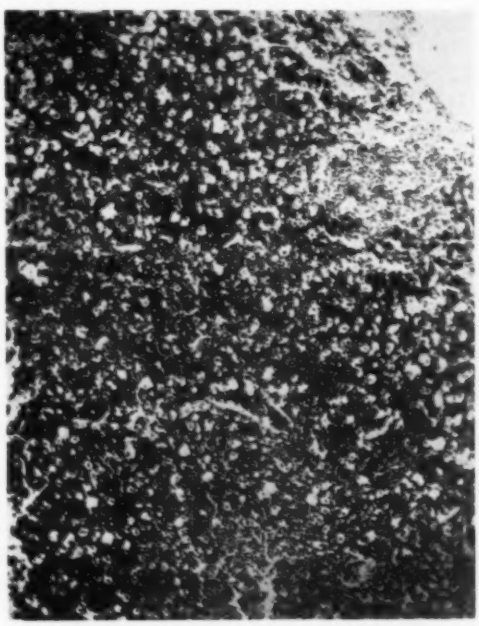

FIG. 553. Section of large thymoma showing predominance of thymocytes (No. 34). (× 78.)

name he remarks that "it is doubtful whether a malignant tumour of the thymus associated with myasthenia gravis has been reported". I would suggest that the term 'malignant' has been too

rigidly interpreted. In my view all these tumours are in a sense malignant, for they behave quite differently from the truly benign adenoma, such as

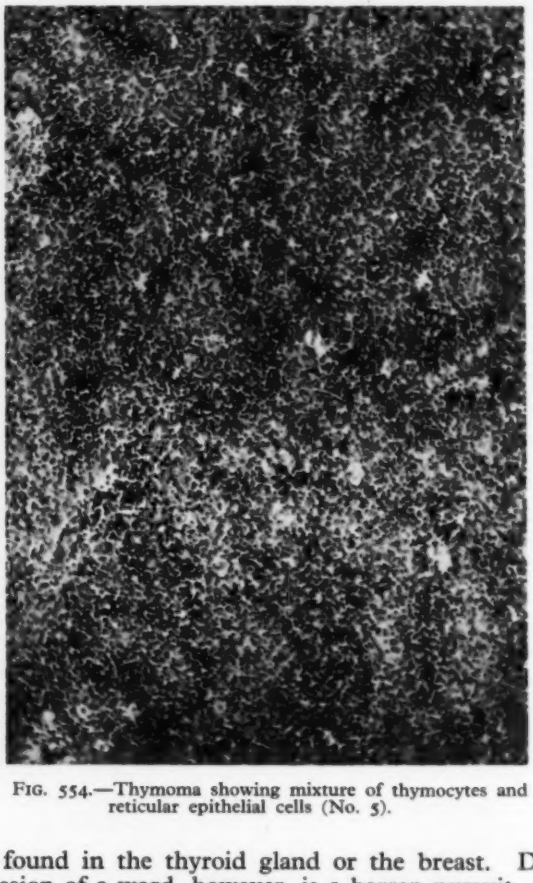

FIG. 554.—Thymoma showing mixture of thymocytes and reticular epithelial cells (No. 5).

is found in the thyroid gland or the breast. Discussion of a word, however, is a barren pursuit. It is better to observe how these tumours behave. Firstly, they invariably provoke a dense fibrous reaction in the tissues in their neighbourhood. They are invested with a thick fibrous capsule, though the proliferating cells within tend to break through in places, and they show thick fibrous trabeculæ in their substance. This reactionary fibrosis results in close adhesion, as already described, to pleura, pericardium, lung, aorta, or large vein according to the situation of the tumour. Secondly, I have no doubt that actual infiltration sometimes occurs. This was found in one of A. L. d'Abreu's patients (No. 46), where the lung was invaded, so that it was impossible to remove the whole of the tumour, and I have occasionally had to abandon an operation for the same reason.

Thirdly, secondary tumours sometimes form in the neighbourhood of the primary tumour. This was found in the patient I have already mentioned (No. 34), who had an enormous thymoma of long standing (*Fig.* 555). Here several daughter tumours were found projecting into the pleura and on the underside of the diaphragm. There was also metastatic growth in lymph-nodes in the cervical, both axillary, mediastinal, cœliac, and upper para-aortic groups, and also in the omentum. The round cells or thymocytes predominated in this tumour. It is true that metastases in lymph-nodes are unusual and distant metastases in other organs through the blood-stream have not yet been found, but it

FIG. 555.—Enormous thymic tumour with daughter tumours below diaphragm (No. 34; specimen in R.C.S. museum).

is not true that thymomas never metastasize, as has often been stated.

Fourthly, removal of a primary thymoma can be followed by widespread recurrence after a long interval. I referred earlier in this lecture to the second tumour removed in the series. This was in a man of 37 who had suffered for three years from fairly severe myasthenia gravis. At operation in May, 1942, a small apparently encapsulated tumour (*Fig.* 556) was removed with some difficulty, and the patient recovered after a rather stormy post-operative period. His myasthenia never showed any great improvement, but

FIG. 556.—Thymoma removed 1942 (No. 2). Weight, 19 g. (× ½.)

he was not obviously worse for several years. Eventually, six years after operation, he was found to have a large pleural effusion. When this had been removed, extensive masses of growth were demonstrated in the pleura and in the anterior mediastinum (*Fig.* 557), the latter projecting upwards even above the suprasternal notch into the neck. A biopsy from this showed the same pure epithelial structure as that of the original tumour. Temporary improvement was obtained with deep X-ray therapy, but the man died seven years after he was first seen.

Fifthly, although most histological reports state that "there are no obvious signs of malignancy",

it is sometimes admitted that the tumour cells show numerous mitoses. This was reported in a patient of A. L. d'Abreu, a woman of 54, who had suffered from myasthenia gravis for eighteen months. A large thymic mass was removed with great difficulty, portions of both right and left pleuras and of the pericardium being removed, together with the left innominate vein. It was a heroic operation, but the patient died on the seventh post-operative day. The tumour consisted of "large irregular cellular islands in a dense cellular stroma. The islands consist of large palely staining epithelial cells with big vesicular nuclei. These cells show a number of mitoses."

Another patient operated on by Ian Hill (No. 43) had a short history of myasthenia gravis with a small tumour in the anterior mediastinum. This rapidly increased and a nodule appeared above the suprasternal notch. A biopsy from this gave a section of "a malignant anaplastic growth".

Whether tumours with these characters are called 'malignant' or not does not very much matter; but obviously the problem of their treatment cannot be simply solved by a routine surgical removal. Sometimes, indeed, this may succeed, but, if so, it is by luck rather than by design.

Silent Thymomas.—Examples of thymomas without symptoms of myasthenia gravis, or 'silent thymomas', are uncommon, but their general characters are similar to those I have already described for the active tumours.

The tumour shown in *Fig.* 558 was contributed by Oswald Tubbs. The tumour was discovered in a young man during mass radiography in 1949, and its X-ray appearance is exactly the same as that of a typical thymoma with myasthenia. It was removed without difficulty, but recurred in 1953 and was then inoperable. It was reported as "a diffuse carcinoma of the thymus of lympho-epitheliomatous type". Similar tumours have been removed by Norman Barrett and and A. L. d'Abreu. Again their position and histology were the same as those of the active tumours, and their thymic origin cannot be in doubt.

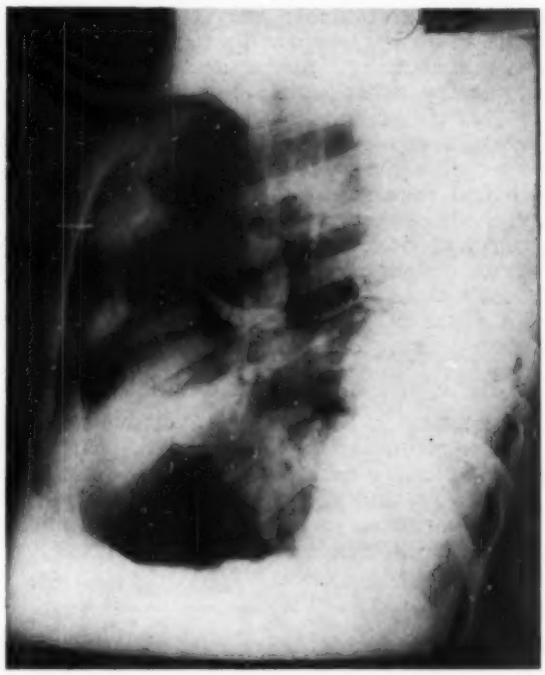

FIG. 557.—Recurrent thymic tumour in anterior mediastinum six years after removal of primary tumour (No. 2).

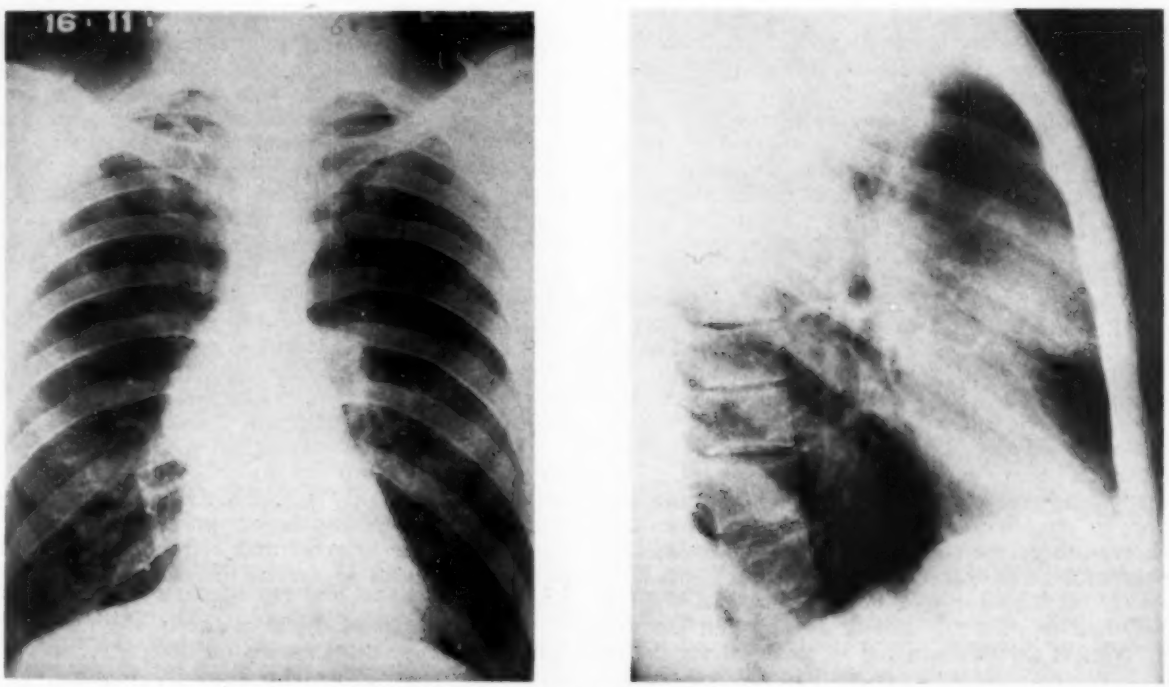

FIG. 558.—'Silent thymoma', anteroposterior and lateral views (Mr. Oswald Tubbs's patient).

It may be that some of these tumours would produce symptoms of myasthenia if they were allowed to remain in the body. As evidence of this there is the example of an eminent member of our profession who came to me in 1950 with three months' history of severe and progressive myasthenia gravis and showing a mediastinal shadow (No. 29). Radiotherapy was begun, but the patient very soon died with respiratory paralysis. Post-mortem examination showed a very large thymoma involving the root of a lung with calcification in its centre, which had been seen in the lateral view on radiography. It is very difficult to believe that this tumour had been present for only three months. I venture to suggest that the silent thymomas are essentially the same as those with myasthenia, but that a phase of inactivity sometimes precedes the the development of symptoms.

CONCLUSION

The pattern of the disease, of which I have tried to give a picture, is a complex one. Myasthenia gravis is in itself a terrible disorder, most distressing to its victims, and if complicated by the presence of a thymic tumour its treatment becomes a difficult problem indeed, demanding an expert team for its application. Physician, surgeon, radiologist, radiotherapeutist, and nursing staff, all have their important parts to play. The association of myasthenia gravis with a thymic tumour is not so rare as was formerly supposed. Reasonable success in treatment can, I submit, only be attained at the present time in the way I have tried to indicate.

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THE PRESENT STATUS OF RENAL ANGIOGRAPHY*

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IN urology we enjoy better diagnostic facilities than in any other branch of deep surgery; that does not absolve us from a constant effort to improve them. We already gain much assistance from our radiological colleagues, and in renal angiography we have another radiological diagnostic aid which has great possibilities and which is in some instances conclusive. The time seems ripe to consider its uses, and to discuss not only when it is indicated but what are its limitations.

Historical.—The pioneer of lumbar aortography was Reynaldo dos Santos, who reported a series of 300 cases in 1929 (dos Santos, Lamas, and Caldas, 1929). There was an element of danger in his procedure because the contrast medium used was 80 per cent sodium iodide; if this went into the superior mesenteric artery in any quantity it caused thrombosis and gangrene of the bowel. The investigation was repeated in dogs by Henline and Moore in 1936 with the same contrast medium and with even more disastrous results. It was with this background of danger that Nelson (1942) and later Doss (Doss, Thomas, and Bond, 1942) and Wagner (1946) had to contend, and it showed considerable courage that they persevered in their efforts. The use of organic iodine preparations instead of sodium iodide has abolished nearly all the dangers. Griffiths (1950) reported the first series of cases in England, using diodone, 70 per cent. It has now been carried out in more than 200 cases at Middlesex Hospital with no mortality and few complications.

Routes.—There are two routes of approach to the abdominal aorta for this investigation, the lumbar and the femoral. In the lumbar approach the needle is entered below the 12th left rib about four finger-breadths from the midline. It is passed forwards, inwards, and upwards to strike the side of the first lumbar vertebra. Its direction is then changed to become less oblique, and it is advanced towards a marker placed over the first lumbar spine with the stylet withdrawn; it glides past the side of the vertebral body and enters the aorta with a sensation not unlike that of puncture of the spinal theca. The needle is kept clear by injections of saline until the contrast medium is injected.

In the femoral approach, described by Pierce in 1951, the femoral artery on either side is punctured through the skin by a special trocar and cannula; through this a length of polythene tubing is passed into the external and common iliac arteries and up the aorta as far as the origin of the renal arteries.

After a trial of both methods we favour the lumbar route as being easier, quicker, and less prone to failure or complications than the femoral. The femoral route is indicated if an aortic aneurysm is suspected; there may also be difficulty in using the lumbar route when the patient is so fat that the 15-cm. needle will not reach the aorta, but the aorta of a man weighing 21 st. has been punctured by this route.

* A lecture given at the Royal College of Surgeons of England on Oct. 27, 1954.

Dangers.—Let us consider the theoretical dangers of the lumbar route. Extravasation of blood has been feared but has not occurred to any serious extent; on some occasions when operating on the left kidney shortly after aortography I have found a little clot, but usually the tissues are only stained. Rupture of the aorta has not been seen even in atheromatous cases. Injection into or around the aortic sheath has occurred in a few cases; it causes post-operative pain but the contrast medium is absorbed within the hour (Griffiths, 1950).

When using the femoral route there has occasionally been perforation of the external iliac artery with some extravasation which duly absorbed. Local hæmatoma formation at the site of puncture has also occurred.

The general effects of injecting 30 ml. or even 60 ml. of 70 per cent diodone rapidly into the circulation must be foreseen. Some patients are sensitive to iodine in any form, and before doing an excretion pyelogram we carry out a sensitivity test with a small amount of diodone. As every patient who has an aortogram has already had an excretion pyelogram we have avoided the hazard of iodine reactions.

The only serious general reaction encountered was in a man of 51 with normal kidneys to whom a double injection was given. He developed anuria which lasted for six days, but recovered completely under treatment by an intragastric drip of glucose and arachis oil.

Causes of Failure.—Apart from these possible complications the main cause of failure to obtain good renal angiograms by the lumbar route is a faulty position of the needle point. If it is too high the cœliac axis and its branches will be filled instead of the renal arteries, and if too low the bulk may go into the superior mesenteric. No undue disturbance follows in either of these cases when diodone is used. Using the femoral route there has been failure when the catheter went into the circumflex iliac artery, and there are some iliac arteries which are too tortuous to be catheterized.

Technique.—The technique we employ has been described by Whiteside (1953). We prefer the patient to have a general anæsthetic and the modern anæsthetist can arrest respiration during the exposures. Three needles, varying in length from 15 cm. (16 s.w.g.) for adults down to 9 cm. (20 s.w.g.) for children, are provided in the set. The 30-ml. diodone syringe has a metal cover for protection of the hand in case of breakage during the rapid injection, and all the pressure tubing is reinforced and joints are wired (*Fig.* 559). Several saline syringes are needed. Just as the injection is made manually, so the film changing is also done by hand. The patient lies prone on a wooden tunnel, and the original model made by the hospital carpenter at a cost of about £5 over four years ago is still in use. An assistant stands on each side, one to withdraw the exposed film, the other to insert the next one. We expect to get four films at each injection, and it is obvious that accurate timing and good teamwork are required. A practice run without injection or exposure is a great advantage if new assistants are

FIG. 559.—Instruments for lumbar aortography. 30-ml. syringe with metal cover, flat-topped piston and finger-grips, for diodone. 20-ml. syringe for saline. Needles 15-cm., 16 s.w.g., for adults; 9-cm., 20 s.w.g., for children; 13-cm., 18 s.w.g., for adolescents.

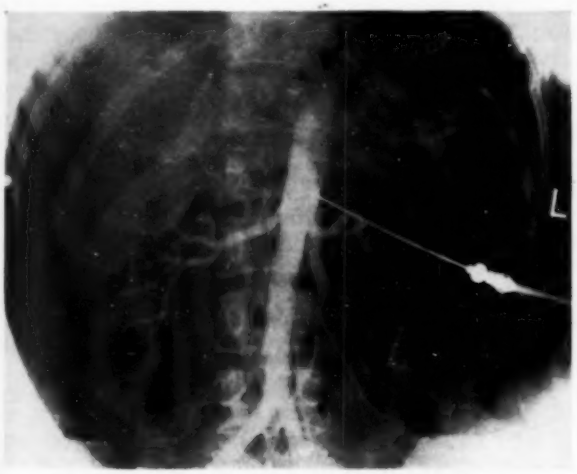

FIG. 560.—Normal renal angiogram, second film. The renal vascular pattern is normal and the arteries are of good size. The superior mesenteric artery is also filled.

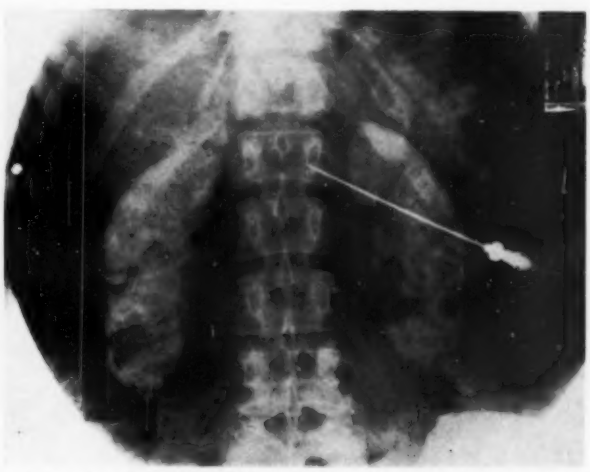

FIG. 561.—The fourth film of the same series, showing the nephrogram.

helping. The needle is left in position, saline being constantly injected, whilst the films are processed, and if necessary a second injection is given. This will give an incidental excretion pyelogram.

There is no doubt that a more detailed study of the renal circulation in health and disease can be made if an automatic film changer is available. In Leeds Professor Johnstone has one by which twelve films can be exposed in one case at varying controlled intervals. The machine we should like would cost £12,000 and up to now we have not got it. I am, however, experimenting with a cheaper home-produced model costing about £200 which is proving satisfactory.

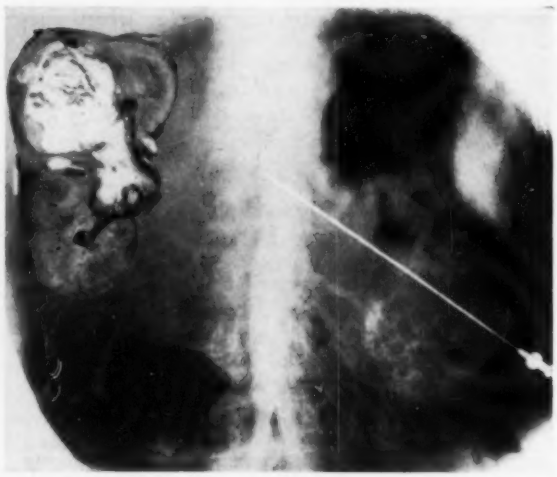

FIG. 562. - Angiogram of an adenocarcinoma of the left kidney showing pooling of the contrast medium in the tumour. The superimposed kidney shows the extent of the growth (Mr. R. S. Handley's case.)

A B

FIG. 564.—A, Pre-operative, and B, post-operative pyelograms of the kidney shown in *Fig.* 563. Removal of the cyst abolished the space-filling lesion and left a useful kidney.

The Normal Angiogram.—The first film shows the early arterial phase. The main renal arteries are filled together with their interlobar branches and so-called 'arcuate' branches (*Fig.* 560). The second film shows more filling of the renal vessels and is sometimes obscured by filling of the mesenteric arteries. In the third and fourth the more solid appearance of the nephrogram is seen (*Fig.* 561); occasionally renal veins can be recognized. In some cases retrograde pyelography and perirenal oxygen insufflation have also been done at the same examination; the combination of methods is sometimes of value.

FIG. 563.—Translucent area in the nephrogram of the left kidney produced by a solitary cyst.

INDICATIONS FOR RENAL ANGIOGRAPHY

When this work was started we considered that the main indication for an aortogram was when one kidney failed to function on excretion urography and its ureter could not be catheterized for the purpose of a retrograde pyelogram. That is still an important general indication, but the scope of the investigation has been widened.

In my first 100 patients the cases fell into the following groups :—

Renal new growth	21
Hydronephrosis and hydrocalicosis	18
Renal cysts	15
Congenital anomalies	14
Investigation of hæmaturia or pain	12
Tuberculosis	9
Non-tuberculous inflammation	7
Calculous disease	4

These figures give the approximate percentages in which we have found the investigation useful, but we have also used it in cases of hypertension, contracted kidneys, and retroperitoneal tumours. I can best indicate its uses by showing some typical examples, with comparisons where possible with the pyelograms and the specimen.

New Growths and Cysts.—One of the greatest advances made possible by aortography is the accurate pre-operative diagnosis between a renal parenchymal tumour and a solitary cyst. The

distinction is important because whilst new growths need removal, in the case of a cyst there may be circumstances which justify abstention from surgery.

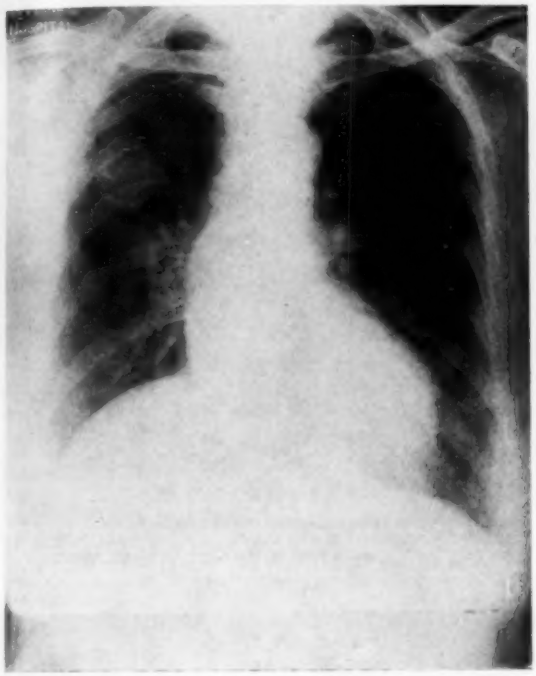

FIG. 565.—Radiographic shadow in the right lung suggestive of a renal metastasis in a woman with hæmaturia.

The typical aortogram of a new growth may show displacement of the vessels near the tumour, but the growth itself presents a mottled appearance due to pooling of the contrast medium in the vascular spaces (*Fig.* 562). This appearance persists in the nephrogram and when seen is diagnostic.

In a solitary cyst the vessels curve around the swelling which is itself avascular and shows as a translucent area in the nephrogram (*Fig.* 563). If the main renal artery is of good size it is possible to excise the cyst and conserve the functioning kidney tissue. The pyelogram before operation shows a space-filling lesion between the upper and middle calices; this space disappeared after operation (*Fig.* 564 A, B).

The exclusion of a renal neoplasm is also of vital importance. A woman of 72 complained of pain in the chest and was found to have a shadow in the right lung very suggestive of a renal metastasis (*Fig.* 565); this was supported by a history of one episode of hæmaturia. Cystoscopy showed a small vesical papilloma, but the pyelogram of the right kidney (*Fig.* 566) showed compression of the upper calices not unlike that of a new growth. The aortogram gave conclusive evidence of a normal right kidney (*Fig.* 567). The shadow in the chest was caused by a bronchial carcinoma.

Failure to recognize a new growth may have serious consequences. In a man of 45 the smooth spherical appearance of the filling defect in the upper calix led to a diagnosis of a cyst; there had been no hæmaturia. Further investigation was postponed for a year when an aortogram (*Fig.* 568) showed a small area of pooling in the region of the filling defect; the contrast medium also filled a metastasis at the right side of the 11th dorsal vertebra, fed by a lumbar artery. Both the pooling and the metastasis

FIG. 566.—Pyelogram in the same case as *Fig.* 565. The compression of the right upper calix is consistent with a renal neoplasm.

FIG. 567.—Renal angiogram in the same patient as *Fig.* 566. The vascular pattern of the right kidney is normal and belies a new growth. Note the excretion pyelogram produced by a second injection of diodone.

were confirmed in the third film of the series. The kidney was removed (*Fig.* 569), but the growth had invaded the vein and the spinal metastasis did not

respond to X-ray treatment. I must add that a re-examination of the original radiographs showed

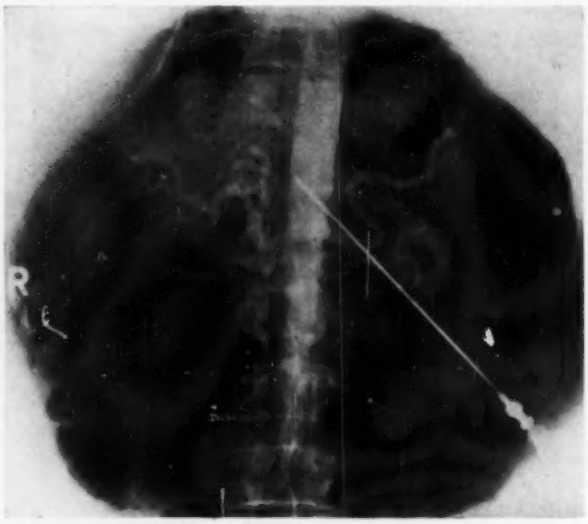

FIG. 568.—Small area of pooling in the left kidney (seen just above the outer half of the needle). The contrast medium has also entered a metastasis in the right side of the 11th dorsal vertebra, fed by a vertebral artery.

the early signs of the metastasis, so the ultimate prognosis was not affected by the delay.

We have shown elsewhere (Riches, Griffiths, and Thackray, 1951) that absence of excretion on an intravenous pyelogram in renal new growths often indicates invasion of the renal vein, which worsens the prognosis. We have found no similar prognostic aid from angiography; in the previous case the primary growth was comparatively small but it was of grade 2 malignancy and venous spread had occurred; the patient is dead. The growth shown by the large area of pooling in *Fig.* 570 had spread into the vena cava, from which it was removed. It

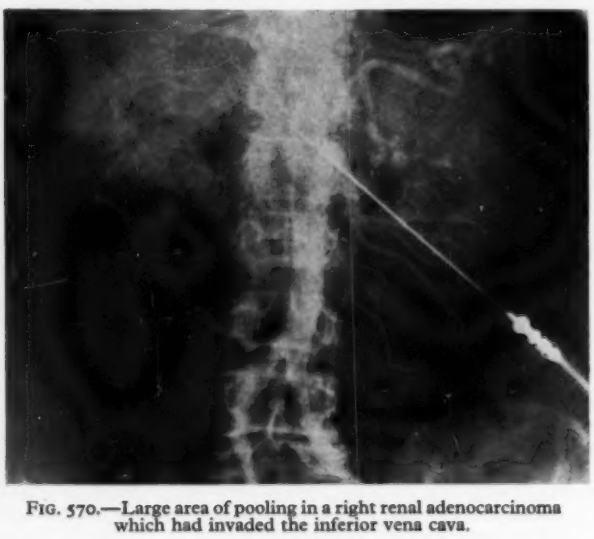

FIG. 570.—Large area of pooling in a right renal adenocarcinoma which had invaded the inferior vena cava.

was of low-grade malignancy and the patient is alive and well more than two years later. Both had post-operative X-ray treatment. The chief prognostic factors in these tumours are still the histological grading and the presence of venous involvement,

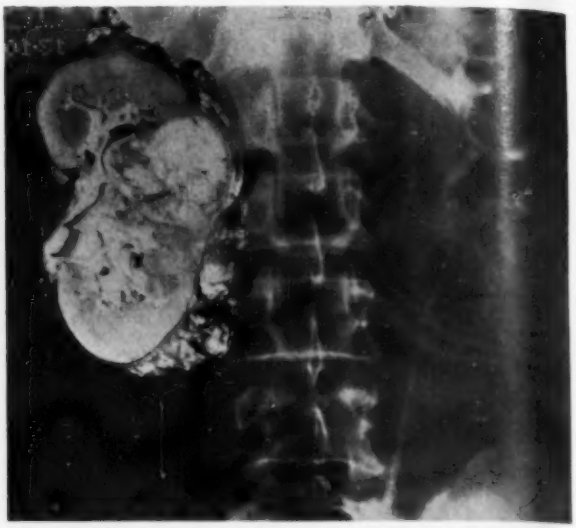

FIG. 569.—Pyelogram of the same patient as *Fig.* 568. The circular filling defect in the upper calix corresponds with the relatively small growth seen in the superimposed kidney.

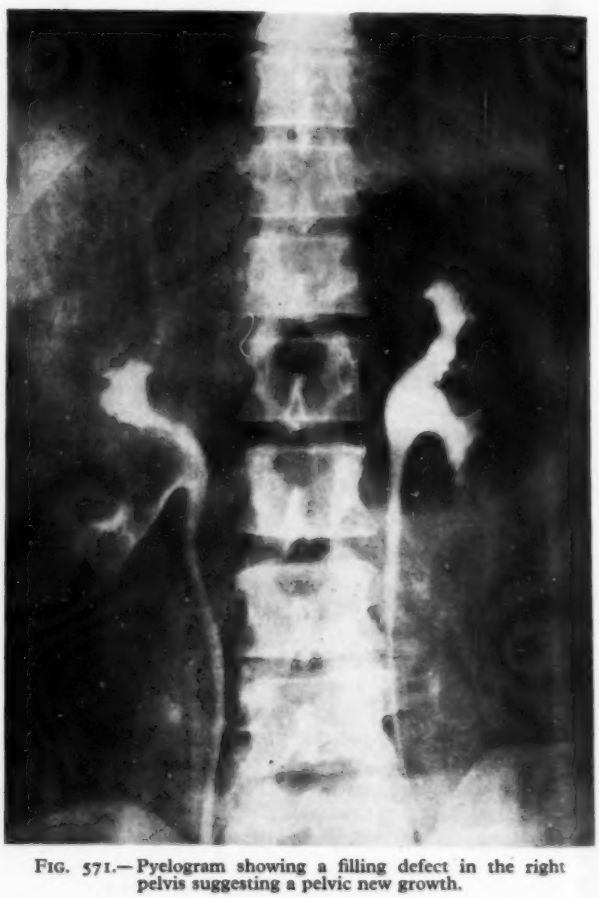

FIG. 571.—Pyelogram showing a filling defect in the right pelvis suggesting a pelvic new growth.

neither of which are shown by aortography. It should, however, be possible by this investigation to detect an early cortical neoplasm before it has reached

a calix. In a man of 48 in whom the pyelogram was inconclusive there was a small area of pooling in the right kidney, and the specimen showed a relatively early growth on the anterior surface, but we are still hoping to find one at an earlier stage than this.

FIG. 572.—Angiogram in the same patient as *Fig.* 571 showing a depression in the nephrogram but no pooling in the neoplasm. The vessel above the right renal artery is the hepatic artery.

In only one case have both the pyelogram and the aortogram suggested the presence of a cyst when there was in reality a solid new growth. This was in the man of 21 st. already mentioned; because of his bulk the radiographs were poor and I decided that exploration would be the safer course, and so it proved.

Renal Pelvic Tumours.—The papillary transitional-cell carcinoma of the renal pelvis gives no specific aortographic pattern and is best diagnosed by the pelvic filling defect shown by pyelography. If the growth is very large it will displace the kidney outwards and elongate the renal artery, just as will a large hydronephrosis, but in the latter case the nephrogram will be less dense. If the tumour, whether papillary or solid, blocks the ureter it will give the changes of hydronephrosis with an absent or faint nephrogram. If a pelvic tumour invades the parenchyma it is usually avascular and shows small vessels and an absent nephrogram in the invaded area. In one patient we diagnosed a pelvic carcinoma on the evidence of the pyelogram (*Fig.* 571). Renal angiography showed a defect in the nephrogram but no pooling, and the diagnosis of a pelvic tumour seemed to be verified (*Fig.* 572). Accordingly she had a nephro-ureterectomy instead of a nephrectomy but the kidney showed a renal adenocarcinoma invading the pelvis instead of the reverse (*Fig.* 573). All the solid pelvic tumours have proved to be much more malignant than the papillary growths, just as they are in the bladder.

Benign growths of the kidney are so rare that we have had little experience of their angiographic appearance. In a case of extensive hæmangioma of a pyramid the aortogram appeared to be normal.

Polycystic Disease.—In congenital cystic disease of the kidneys the aortogram gives little information which is not obtainable by other methods. A typical picture shows a poor blood-supply with the smaller vessels spread around the cysts, and a patchy cotton-wool appearance in the nephrogram (*Fig.* 574). The changes are bilateral, but usually more advanced on one side. If there is extensive

FIG. 573.—Later stage of *Fig.* 572. The superimposed kidney shows that the depression in the nephrogram is below the neoplasm; there is no pooling.

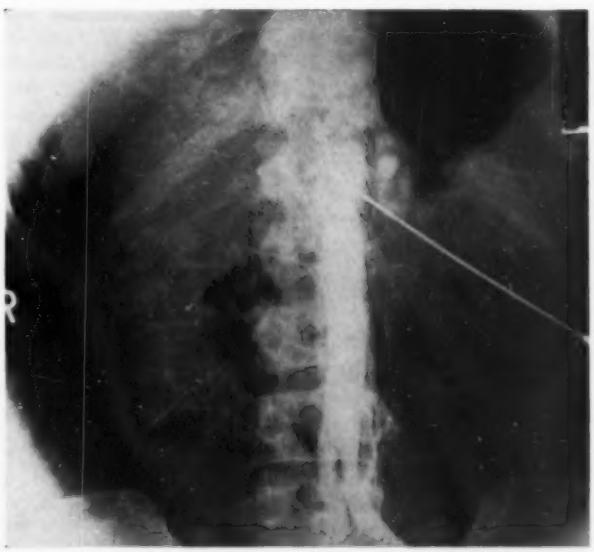

FIG. 574.—Angiogram in a case of polycystic kidneys, more advanced on the right. The renal arteries are small and their branches spread around the cysts. The nephrogram has a patchy appearance.

bilateral disease with bad renal function aortography should not be done.

Hydronephrosis.—By angiography in this condition we obtain information about renal function and knowledge of the presence or absence of accessory vessels. As a test of renal function the aortogram is more reliable than the intravenous pyelogram. The degree of reduction in size of the main renal artery and in number of the peripheral branches is a good indication of the functional activity of the kidney. The density of the nephrogram is also an indication of function provided that the point of the needle is equidistant from the right and left renal arteries.

Johnstone (1952) has pointed out the fallacy of interpreting a dense nephrogram as evidence of good function if the major part of the contrast medium has been injected into the artery of that kidney. A plastic operation on a hydronephrotic kidney will only succeed if there is an adequate blood-supply. In a woman of 34 with a right hydronephrosis the blood-supply appeared adequate and a plastic operation of the Anderson-Hynes type was performed. There were no aberrant vessels either seen on the aortogram or found at operation (*Fig.* 575). The excretion urograms before and more than a year after operation show that a kidney of good function had been preserved (*Fig.* 576, A, B). Abnormal vessels will show on the aortogram unless they are obliterated. In the case illustrated in *Fig.* 577 a large artery arising from the aorta was found together with a vein entering the left ovarian; they formed a pedicle half-an-inch broad. The main renal vessels were very small in the aortogram and the nephrogram was faint. The

FIG. 575.—Nephrogram and right pyelogram in a case of hydronephrosis. The right renal artery is of adequate size although the nephrogram is less dense than that of the left kidney.

A B

FIG. 575.—The same patient as *Fig.* 575. Excretion pyelograms before (A) and one year after (B) plastic operation on the renal pelvis.

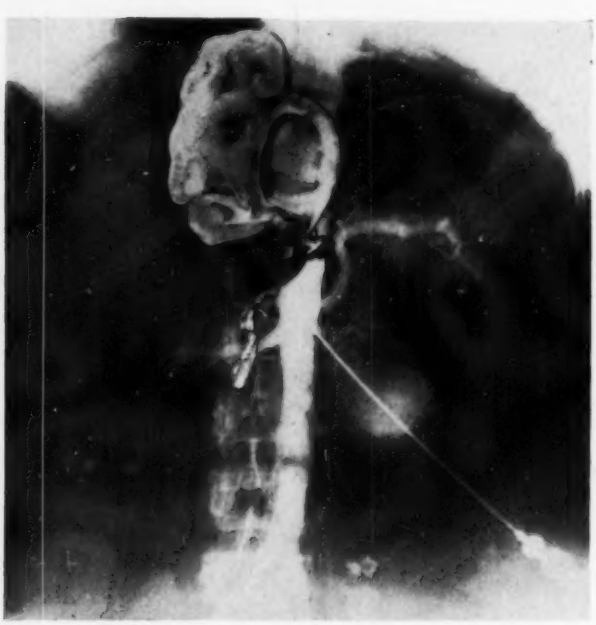

FIG. 577.—Left hydronephrosis. The aberrant artery going to the lower pole is shown passing behind the ureter. The small size of the left renal artery determined the removal of the kidney. (Kidney seen from behind.)

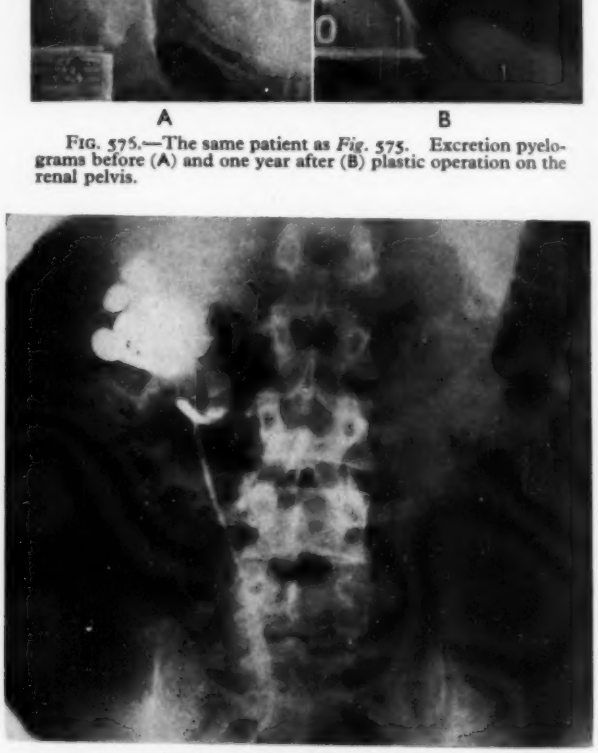

FIG. 578.—Pyelogram in a case of right hydronephrosis showing a twist in the upper end of the ureter.

kidney was therefore excised; the specimen has had only a thin slice cut from its posterior aspect in order to show the aberrant vessels; its thickness of cortex was only half-an-inch.

The presence of aberrant lower polar vessels on the radiograph is no proof that they are a cause of the obstruction, but such proof can sometimes be obtained. In a man of 34 the pyelogram showed a pelvic hydronephrosis with a typical twist just below the pelvi-ureteric junction (*Fig.* 578). The aortogram with the ureteric catheter still in position gave a pretty demonstration of the catheter hooking over an artery to the lower pole of the kidney (*Fig.* 579). Despite the poor blood-supply to the right kidney I was tempted to do a plastic operation, but it failed and I had to remove the kidney.

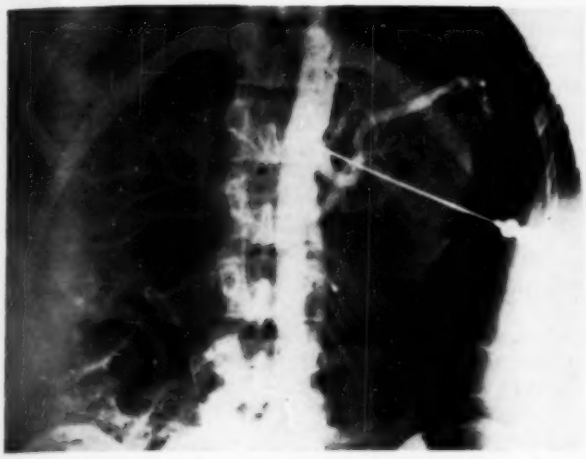

FIG. 579.—Angiogram in the same case as *Fig.* 578. The ureteric catheter hooks over the lower polar artery to the right kidney.

When the vessels to a hydronephrotic kidney are small and the other kidney is normal, nephrectomy is indicated rather than an attempt to repair. In the case of hydronephrosis shown in *Fig.* 580 the left renal vessels were minute; the pre-operative blood-pressure was 290/140. The excised kidney showed fibrosis with marked hypertensive vascular thickening. More than a year later she was free from headache and giddiness, her heart was smaller, and the blood-pressure was 180/100. It is an interesting speculation whether renal angiography, by showing the relative size of the renal arteries, will give the best indication for nephrectomy in unilateral renal hypertension, but it must be remembered that in hydronephrosis as the kidney destruction increases the renal arteries diminish in size.

It will have been noticed that a translucent area in the nephrogram can be caused by various conditions; a cyst, a pelvic new growth invading the parenchyma, and hydronephrosis can all give it, and their differentiation depends not on angiography alone but on its correlation with pyelography, both excretion and retrograde.

Hydrocalicosis.—Renal angiography is again of great practical use when there is a localized dilatation of a calix, or in any condition for which partial nephrectomy is contemplated. It is possible to see before operation if there is a vessel going to the affected part which can be safely ligated, and in some instances such ligature is followed by an area of cyanosis which marks out the part to be excised.

Congenital Anomalies.—The numerous congenital anomalies to which the urinary tract is prone will repay study by aortography. In a child of 6 with a left hydro-ureter and recurrent pyelitis the absence of the right kidney was finally proved by aortography and conservative surgical treatment was adopted for the left. If a kidney is absent from the loin one must not forget the possibility of its presence in the pelvis. In such a case the accurate localization of the arteries to the ectopic kidney is of great help in its removal should that be necessary (*Fig.* 581).

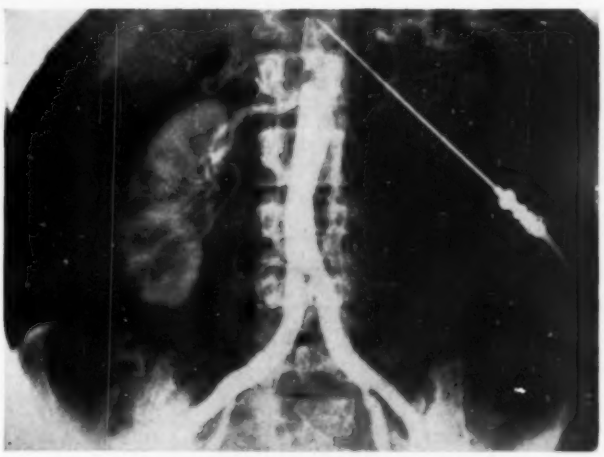

FIG. 580.—Left hydronephrosis with hypertension. The small left renal arteries curve round the dilated pelvis and there is no nephrogram.

FIG. 581.—Pelvic ectopic kidney. Arteries from the bifurcation of the aorta and the left internal iliac supply it. The kidney was dilated and the position of the arteries was verified at its removal.

A double kidney usually has a double blood-supply; its size and distribution may be a factor in deciding upon heminephrectomy or total nephrectomy or conservative treatment (*Fig.* 582).

Stone.—Apart from those cases where stone is associated with a congenital anomaly the main use of angiography is where the stone lies in a dilated calix

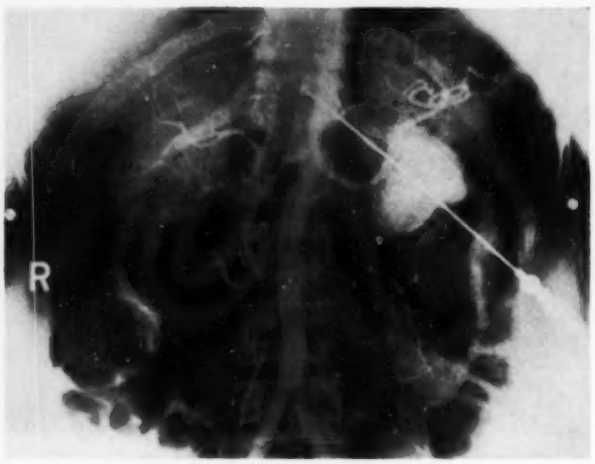

FIG. 582.—Left double kidney with a stone in the upper half. The artery to the upper half, seen below the splenic, was small, and that to the lower half adequate. Left heminephrectomy.

and it is proposed to do a partial nephrectomy. The extent of the blood-supply to a calculous kidney may be a factor in deciding on its conservation or ablation.

Tuberculosis.—The results of angiography in this disease have been somewhat disappointing as so far we have failed to show cortical cavitation by its means. In some cases it was hoped to show the defects in the nephrogram described by Weyde (1951) and to utilize the method in the selection of cases for partial nephrectomy. As a rule we have found that the nephrogram gives little help in this direction and that the pyelogram gives more accurate information. Even that will not show the extent to which tubercles may spread in the pelvis and down the ureter. In other cases with cavitation known to be present from the pyelogram the aortogram has differed little from the normal. I consider that the full benefit of renal angiography in tuberculous disease can only be reaped with an elaborate film-changing mechanism.

Contracted Kidney.—We have investigated several cases where the kidney was very small and there is room for further work in this field. A man of 25 with right loin pain had a blood-pressure of 190/100. The urine was sterile, there was no excretion on the right side on excretion urography and the retrograde pyelogram showed a small atrophic kidney on that side. The aortogram gave evidence of a good blood-supply on the left, but practically none on the right; there was, however, a very faint nephrogram of a small kidney. At operation I removed a small hydronephrotic kidney; sections showed the changes of old pyelonephritis. Seven months later the blood-pressure was only 120/80.

Miscellaneous Cases.—Retroperitoneal tumours can be distinguished from renal swellings by aortography, but their outline is more clearly shown by presacral oxygen insufflation combined with pyelography. We have not yet encountered a case of renal infarction; it should be detectable by the avascular area in the nephrogram. We have investigated a number of cases of unexplained hæmaturia but have gained no further help than the knowledge that the kidneys were anatomically normal.

CONCLUSIONS

Renal angiography is a safe procedure, and the technique can be mastered fairly easily. It can be done in any general hospital which has a good diagnostic X-ray department. It is an essential part of the investigation of a space-occupying lesion in the kidney, of hydronephrosis, of congenital anomalies, and of any condition for which partial nephrectomy is contemplated. It is often desirable in suspected renal hypertension.

The contra-indications to its use are iodine sensitivity and uræmia.

I do not think the limits of its use have yet been reached; its scope will be increased by improvements in film-changing mechanisms and in X-ray technique generally. It does not replace the standard well-tried urological investigations, but is complementary to them.

I must pay tribute and give thanks to my colleagues Dr. C. G. Whiteside, in the radiodiagnostic department, and Mr. I. H. Griffiths, in my own department, at Middlesex Hospital for their unbounded enthusiasm and skill in promoting this work. I must also thank Mr. M. Turney for reproducing the photographs.

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PERINEAL CIRSOID

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"The swelling also is doughy and very compressible but when the pressure is removed, the blood enters it with a whiz and thrill, not with the distinct pulsating stroke that is found in aneurism."—J. E. Erichsen on aneurism by anastomosis (1869).

CIRSOID aneurysms most commonly occur on the scalp and in relation to the cortex of the brain and are comparatively rare elsewhere. A typical example on the scalp is shown in *Fig.* 583. I extirpated this eighteen years ago and it has not recurred. Elkin (1946) suggested that the appearance of these scalp cirsoids may have given rise to the legend of the serpents on the head of Medusa. Examples of subcutaneous cirsoids occurring in regions other than the scalp have been recorded; in the neck (Cole and

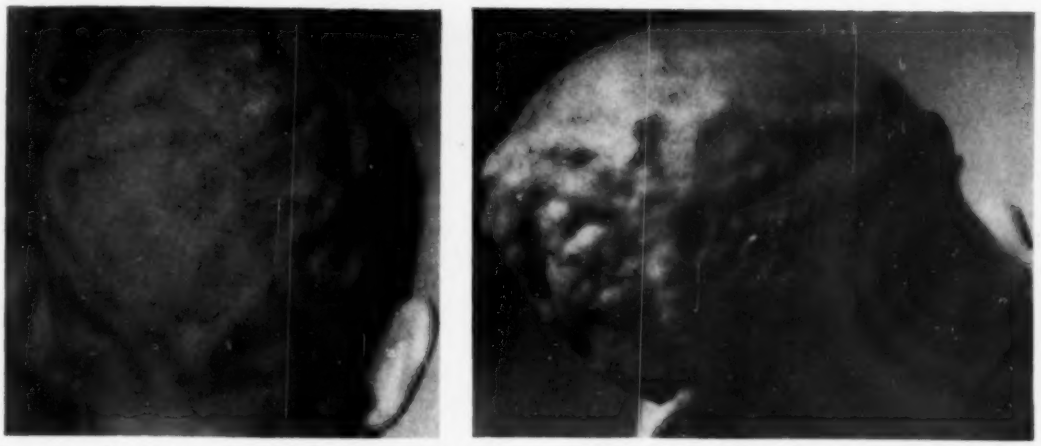

FIG. 583.—Cirsoid aneurysm of scalp of a man aged 20, successfully treated by excision, January, 1936. This patient was seen well and without recurrence, March, 1955.

FIG. 584.—Perineal cirsoid in a man aged 27.

Hunt, 1948), on the lip (Marshall, 1937; Cole and Hunt, 1948), in the pubic region (Bertola, Moreryra Bernan, and Parodi, 1946), and Sir John Bland-Sutton (1917) mentions that the largest which had come under his notice occupied the perineum of a lad, aged 19.

With his wide knowledge of comparative anatomy Sir John Bland-Sutton saw the resemblance between cirsoid aneurysms and the vascular arrangements of the rete mirabile in the forelimbs of sloths, the tails of spider monkeys, and the subpleural plexuses of the cetaceans.

Known by a variety of names, such as plexiform or racemose angioma of arterial, venous, or mixed varieties, aneurysmal varix, varicose nævus, aneurysm by anastomosis, aneurysmal or pulsating angioma, and varicose, plexiform, or cirsoid aneurysm, the subcutaneous lesions fall into the same two groups into which Cushing and Bailey (1928) classified the blood-vessel tumours of the brain, namely the angiomatous malformations and the hæmangioblastomata. Elsewhere (Rogers, 1936) I have recorded examples of both varieties occurring in the scalp. Searby (1932) has clearly shown that all these vascular lesions contain abnormal connecting channels between their arterial and venous components and are thus all examples of arteriovenous aneurysms.

I am indebted to my colleague, Mr. J. F. E. Gillam, F.R.C.S., for kindly giving me the opportunity to deal with the following example of a perineal cirsoid in which there was fibrous and fatty tissue along with a multitude of ramifying vessels some being quite large channels, many of which were thick-walled arteries.

Case.—A married man, aged 27, a clerk in a Government office, complained of an irritant, hot, and pulsating swelling in the perineum which had been present throughout his life. Profuse perspiration in the area resulted in irritation which was worse when walking and limited his activities, such as playing football. Twice the skin over the mass had broken and there had been profuse bleeding, on one occasion in the form of a jet which necessitated his admission to hospital for its arrest.

FIG. 585.—Angiograms of perineal cirsoid. Same patient as *Fig.* 584.

Examination showed a healthy well-built young man, normal in all respects except for a large perineal swelling extending backwards from the scrotum almost as far as, but not involving the anus (*Fig.* 584). Approximate measurements of the swelling were 7 in. long by 2 in. wide and 3 in. in depth. On palpation it was soft and hot and could be felt to contain large pulsating vessels. The covering skin was pigmented and beset with tortuous veins. When a stethoscope was placed over the mass, a to-and-fro bruit could be heard. There was no evidence of any effect of the lesion on the general circulation. Angiograms obtained from injecting the

femoral arteries, for which I am indebted to Dr. Arthur Jones, of the Cardiff Royal Infirmary, are shown in *Fig.* 585.

AT OPERATION.—The tumour along with some perineal skin covering it was excised under general anæsthesia, the patient being placed in the lithotomy position and receiving a blood transfusion meanwhile. Large vessels were ligated as exposed, but even so there was a good deal of bleeding because of cutaneous vascular connexions which had to be divided. After the vascular mass had been excised the superficial perineal muscles were exposed in the wound. To prevent the passage backwards of the testes into the perineum, a new central perineal point was constructed by stitching the skin to the superficial perineal muscles with thread sutures which were also used to bring the skin edges together. Healing and convalescence were satisfactory. The specimen is shown in *Figs.* 586, 587.

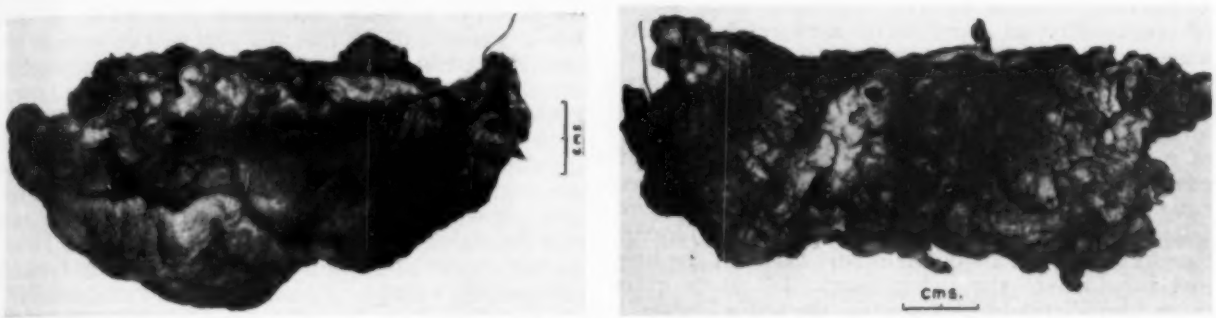

FIG. 586.—Perineal cirsoid after excision. In right hand figure the tumour has been partly opened to show the wide mouths of some of the constituent vessels.

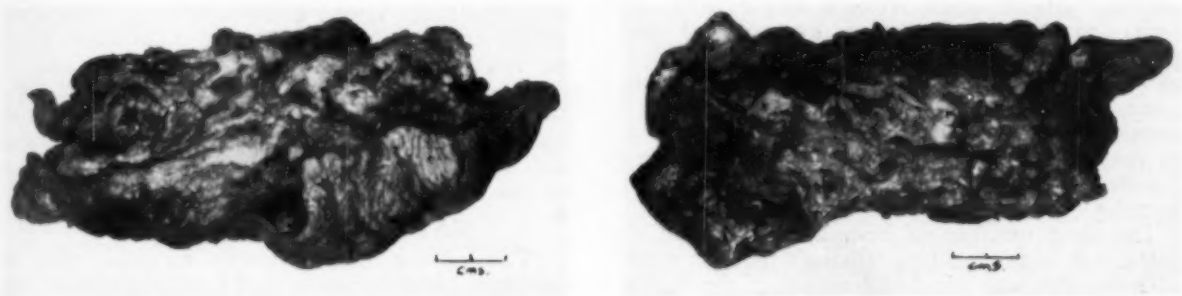

FIG. 587.—Other views of perineal cirsoid tumour to show the tortuous vessels of which it is composed. Many of these are thick-walled arteries.

SUMMARY

Cirsoid aneurysms most commonly occur on the scalp, but are occasionally found elsewhere. An example in the perineum is here reported. These aneurysmal angiomas may be purely developmental, vascular anomalies composed of interlacing masses of vascular channels which are either predominantly arterial, or predominantly venous, or consist of a mixture of both types of vessels or they may contain fibrous and fatty tissue in addition to the vascular elements and be better regarded as hæmangioblastomas. The only satisfactory treatment of either variety is excision.

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ON THE NUMBER OF BRANCHES FORMED BY REGENERATING NERVE-FIBRES

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INTRODUCTION

It has long been known that during the initial stages of regeneration in a peripheral nerve each growing axon above the point of injury proliferates, giving rise to several branches which may invade the distal segment of the nerve. In the present work a quantitative study has been made of the number of sprouts formed during regeneration of motor and sensory nerves in the rabbit. Previous workers have estimated the number of branches that may arise from a single axon. Thus Ranson (1912) found that in cross-sections of the sciatic nerve in the dog just proximal to the lesion (section) " 50 or even more fibres " might be found in the space formerly occupied by one fibre. Perroncito (1907) shows in an illustration 24 branches arising from one fibre, and Cajal (1928) thought it likely that " dozens of branches " might arise from a single fibre. De Castro (1930) saw very many branches on post-ganglionic fibres. Howe, Tower, and Duel (1937) found numerous fibres having three or four branches in the facial nerve of the monkey 44 days after operation. Young (1949) shows an axon giving five branches at the entrance to the distal stump of a rabbit nerve which had been divided and sutured 5 days previously.

The total number of branches formed in the nerve-trunk is not known, although there is reason to believe that the successful repair of the injured nerve depends on this branching. Previous quantitative work on this point has been done on preparations stained to show the myelinated fibres, and no exact estimates are available which include the non-myelinated fibres, other than those made by Davenport, Chor, and Dolkart (1937), and Davenport, Chor, and Cleveland (1939). Moreover there are no figures for the number of axons in a nerve in the very early stages of regeneration, before myelination has begun. Clearly a knowledge of the full extent to which the normal fibre population of a nerve is increased during regeneration would be of great significance. It would lead to a more accurate assessment of the chances of an adequate re-innervation of a nerve distal to any part of it damaged by injury or surgical interference. Further, the average number of branches formed by each regenerating axon could be calculated. The present investigation was started to determine :—

1. The total number of axons formed by all fibres, both medullated and otherwise, at different levels from the lesion and at various stages of regeneration.

2. The effect of the nature of the lesion on the number of branches.

3. Whether motor and sensory nerves differ in the number of branches to which their fibres give rise, as suggested by the experiments of Dogliotti (1935), who found that motor-fibres produced more branches than sensory ones.

4. Whether the size of the parent fibre has any effect on the number of its branches.

In order to study the effects of a lesion on the whole nerve and not just the part in the vicinity of the injury, transverse sections were taken at regular intervals along the nerve, as described later. Three kinds of injury were employed : (1) a simple crush with forceps, (2) severance of the nerve with immediate suture, and (3) crushing the nerve proximally and isolating it from its muscle by severance distally. For the purpose of this investigation the nervus gastrocnemius medialis (n.g.m.) and nervus suralis of rabbits were used as being typical of a muscle nerve and a sensory nerve respectively. All muscle nerves, however, have a large proportion of afferent fibres—about 50 per cent of the total fibre count according to Eccles and Sherrington (1930) in the n.g.m. of the cat. Similarly Ranson and Davenport (1931) came to the conclusion that 40 per cent of the fibres in a muscle nerve in the cat were sensory. There is no evidence that the sural nerve in the rabbit contains any motor fibres. No movement of the muscles, skin, or hair of the leg was produced after cutting this nerve centrally and stimulating the distal segment electrically or by pinching the nerve with forceps.

MATERIAL AND METHODS

The nervus gastrocnemius medialis and the sural and phrenic nerves in full-grown rabbits were used. The animals were of various breeds, but most were of the brindle, English, or chinchilla varieties. Nembutal and ether anæsthesia was employed.

Operative Details.—The nerves were either crushed or cut and sutured. In some animals both sides were operated upon ; in others one side was left as a control. During the separation of the n.g.m. from the nervus tibialis traction was made on the adjacent fascia and not on the nerve itself. The nerve was only dissected free where it was to be crushed or sutured. The crush or suture was made as near the greater trochanter as possible, so that allowing for a sufficient length above the lesion, a good length could be obtained below at biopsy. In the case of the phrenic nerve the crush was made near the lower part of the superior vena cava.

Crushing.—Smooth-tipped watchmaker's forceps were used, the tips being pressed firmly together for 10 seconds on to the nerve. After this procedure the site of the crush looks translucent, but the anatomical continuity of the nerve is not interrupted. In some animals the n.g.m. was crushed proximally and cut near its muscle, the distal end being turned upwards and fixed with fibrin on the fascia covering the adductor muscles of the thigh.

Suturing.—Fibrin was used to keep the nerve ends together (Young and Medawar, 1940). A segment of the nerve was dissected, two or three drops of fibrinogen (human), to which tissue extract had just been added, were then dropped on to the

nerve. When the fibrinogen had nearly clotted the nerve was cut with fine, sharp scissors. In this way handling the nerve-ends with forceps was avoided. When the nerve-ends retracted more than 1 mm. at operation the material was abandoned.

Biopsy and Fixation.—The animals were brought to biopsy at various times from 5 days to 225 days after the operation. The n.g.m. was dissected down to about the point where it begins to branch, just above the gastrocnemius muscle. The sural nerve was removed to half-way down the leg. The whole length of the intrathoracic part of the phrenic nerve was removed. The nerves were placed on cardboard frames, so that only the ends were damaged, and put immediately into Bodian's fixative solution for at least 24 hours.

Sectioning and Staining.—After embedding in paraffin wax in the usual way 5μ transverse sections were taken every 2 mm. along the course of the nerve and transferred to slides. A modification of Bodian's protargol method of staining for nerve-fibres was used.

The problem of finding an adequate silver stain for routine work has yet to be solved. The Bodian method used gives satisfactory results in a regenerating nerve and certainly stains fibres as small as ½μ and less in diameter. It also permits a clear distinction to be made between the axons and nuclei of Schwann (which are stained different colours). With Ranson's silver-pyridine stain, which is probably the best alternative method available, only comparatively short lengths of nerve can be stained in one block and some of the axons are difficult to distinguish from the background. For the normal n.g.m. the figures for axon counts made from silver pyridine preparations (*Table III*) were rather higher than those made from Bodian preparations (*Table I*). On the average, however, 81 per cent of the number of fibres revealed by Ranson's method were counted from Bodian preparations of normal nerves, and it is likely that at least this percentage appears in regenerating nerves.

Table I.—Axon Counts for Normal Nerve to Medial Head of Gastrocnemius stained by Bodian's Method

Rabbit No.	No. Axons High	No. Axons Low	Percentage Increase Distant Counts
1866	333	384	14
2058	460	466	1
2297	358	403	13
2298	399	453	14
2305	350	393	6

Mean of proximal counts = 380
Mean of distal counts = 420
} *Mean all Counts* = 400
Mean increase of distal counts over proximal = 11 per cent.

Photography and Counting.—Photographs were made direct on to bromide paper at a magnification of 750 diameters. The nerve-fibres were then counted on the photographs, each axon being identified on the section under an oil-immersion objective at a magnification of 1000. A mechanical stage was used and the section worked across in several 'cuts'.

Only well-stained sections were used and the identification of the smaller axons was then possible with practice. The smallest axons counted by this method, however, were about ½μ in diameter. The counting error may be judged by the figures obtained by counting the same section twice, e.g., (for the n.g.m.) 602 and 611 and 569 and 565 in two instances. In the sural nerve, where the nerve-fibres are smaller and more closely packed, this error is probably greater. The figures from adjacent levels from the same nerve (n.g.m.) sometimes differed by as much as 10 per cent. The possible inclusion of some old axons, not yet showing signs of degeneration, in counts made in the early stages of regeneration cannot be ignored and will be considered in a later section. Counts were made at the site of the lesion wherever possible, 2 mm. above and below it and at 10-mm. intervals from the lesion. In some cases the nerve was counted every 2 mm. along its course.

Table II.—Axon Counts for Normal N.G.M. stained by Bodian's Method

Distance above Muscle mm.	Axons Present
36	347
20	342
6	344
4	344
2	440 (2 branches)
At entry into muscle	500 (5 branches)

Increase in number of axons = 44 per cent.

Composition of Nervus Gastrocnemius Medialis.—The number of medullated fibres in the rabbit n.g.m. varies considerably. Aitken, Sharman, and Young (1947) found from 354 to 467 fibres in nine different nerves. Causey (1948) and Evans and Vizoso (1951) also give figures for the number of fibres in this nerve, and Dr. Evans has kindly made some unpublished data available. The average of these authors' combined figures works out at 381. These investigators also demonstrated that the number of fibres is much the same at all levels except just proximal to the muscle where the nerve-trunk splits into branches (*see also Table II*). To see whether this was true for all fibres (both medullated and non-medullated) axon counts have been made from material stained by Bodian's method (*see Table I*). Sections taken near the origin of the nerve from the sciatic and near its point of division were counted. A mean increase of 11 per cent in the number of axons was found distally, but this is small enough to be left out of account when computing the number of branches formed during regeneration.

Table III.—Axon Counts for Normal N.G.M. stained by Ranson's Method

Rabbit No.	Axons Present
3020 (1)	529
3020 (2)	482
3247 (1)	467
3247 (2)	459
3260 (1)	536
3260 (2)	489

Mean = 494

The distribution of fibre size in the n.g.m. is bimodal, with peaks at about 7μ and 16μ. The fibre sizes are between 2μ and 20μ, but 73 per cent of the total are more than 10μ in diameter.

Non-myelinated Axons in Normal N.G.M.—Sherrington (1894) described non-myelinated fibres in muscle nerves but noted that they were not so

numerous as in small cutaneous nerves. His evidence was based on the examination of osmic acid preparations. Ranson and Davenport (1931), using silver-pyridine-stained material, found a ratio of myelinated to unmyelinated fibres in the nerve to the vastus medialis muscle in the cat to be 1 in 0·4. Langley (1922) found few non-myelinated fibres in the nerve to the gastrocnemius in cats. No evidence is available as to the number of non-myelinated fibres in

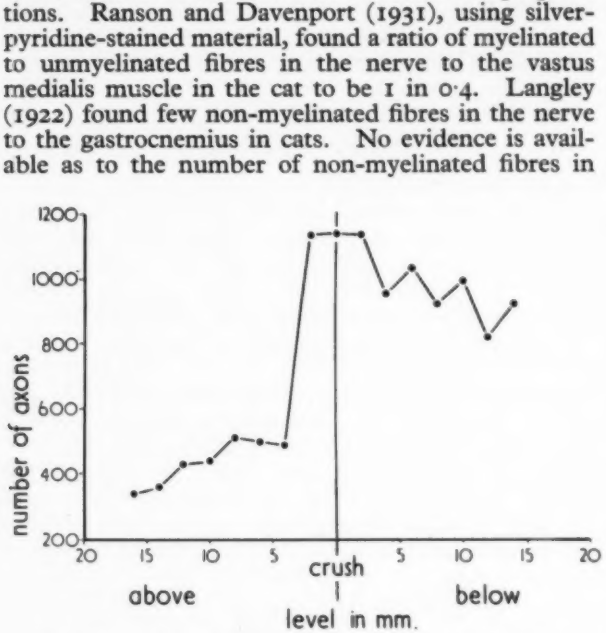

FIG. 588.—Numbers of axons at various levels along a n.g.m. crushed 27 days previously.

the n.g.m. of the rabbit. An attempt has been made to investigate this point by making counts from silver-pyridine sections of the n.g.m. (*see Table III*) and comparing the figures obtained with the counts of medullated fibres made by previous workers (mean = 381). The ratio of myelinated to non-myelinated fibres in the rabbit n.g.m. was found to be 1 : 0·3.

Composition of Nervus Suralis.—This nerve contains from 1300 to 2100 medullated fibres; approximately 50 per cent of sural nerves come within the 1500 to 1700 range (personal communication from Dr. T. A. Quilliam). Eighty-five per cent of the fibres are smaller than 10μ in diameter. The distribution of fibre size is unimodal, the peak being in the 2–6μ range, which accounts for 50 per cent or more of the total number.

From the above figures it will be seen that the n.g.m. has a big proportion of large fibres, while the sural nerve has a large proportion of small fibres. It might be expected, therefore, that if there is any marked difference in the number of branches produced by small and large fibres during regeneration, this should be apparent from an estimation of the axonal population of the regenerating sural and n.g.m. even if sensory and motor fibres are otherwise similar in their behaviour during regeneration.

Composition of Phrenic Nerve.—In the rabbit, Rexed (1944) found this nerve to have a unimodal distribution of its fibres, though this is not the case in cats (Tatesi, 1940). Fernand and Young (1951) examined four phrenic nerves; the mean total number of medullated fibres was 728, and about 80 per cent of them were from 8μ to 12μ in diameter. It was thought that the regeneration of this nerve might throw light on the relationship between the number of branches and size of parent fibres.

RESULTS

Effect of Crushing a Nerve on the Number of its Fibres.—A nerve crushed with a narrow pair of forceps does not show a simple picture of a 'site of lesion', above which the fibres are normal. Indeed a large segment of the nerve presents changes suggesting that it is about or near the crush, however localized the lesion appeared at the time of operation. As one proceeds down the nerve, say 25 days after the crush, there is an increase in the number of axons, which is at first gradual (extending over several millimetres) and then more rapid, until a maximum is reached. Thereafter, proceeding still farther distally, a slow decline occurs. These changes are illustrated in *Fig.* 588.

Site of the Lesion.—Up to 35 days and even 50 days after operation, the approximate site of a crush can be identified. The size and shape of the nerve may be altered, œdema may be present in the region, and this may contain a few nerve-fibres. Sometimes muscle-fibres were adherent to the nerve about the lesion. The staining properties were also changed (darker purple or reddish colour) and the nuclei became more evident in the same region. During biopsy of the n.g.m., part of the sural nerve which runs alongside it was removed with it. This portion of the sural nerve extended from the proximal end of the n.g.m. to just above the site of the crush. Thus transverse sections from the central part of the specimen showed both nerves (n.g.m. and sural)

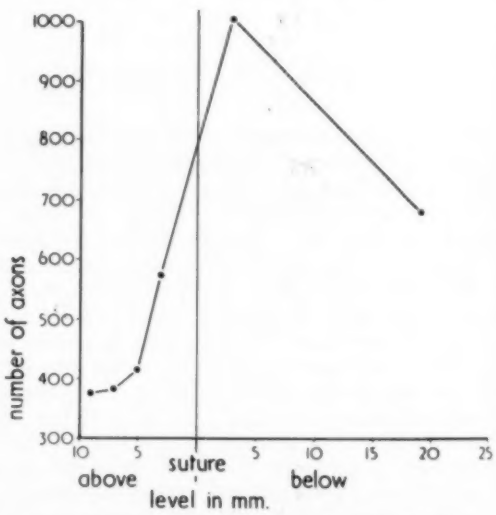

FIG. 589.—Numbers of axons at various levels along the n.g.m. 25 days after a primary suture.

and the first section below this to show the n.g.m. only was at the level of the crush. No other attempt was made to mark the crush, though its position (measured from the proximal end of the nerve) was estimated at biopsy.

An Increase in the Number of Fibres always found above the Lesion.—*Fig.* 588 is based on the results of a 27-day experiment. The estimated site of the crush is indicated, and it will be seen that a substantial increase in the number of fibres occurred above.

With nerves that had been cut and sutured, the sutured area could be identified accurately if a section

was taken through it. The level of such a section made in a 26-day experiment is indicated in *Fig.* 589. This graph also shows the increase in the number of fibres constantly found proximal to a suture.

Regeneration in the N.G.M.—

The First Ten Days.—As a result of crushing a nerve, the fibres adjacent to the crushed region produce a greater number of new fibres by a process of branching. Consequently an increase in the number of fibres is apparent at first just above the crush and later in the distal part of the nerve as the new fibres grow down the empty Schwann tubes. Material obtained as early as five days after crushing already showed many fine, darkly staining axons present above the crushed region. By the tenth day (*Fig.* 599) large numbers of new axons were seen at the level of the crush and some could be traced down 6 mm. below in the two nerves examined at this stage.

Counting the viable axons impossible at this stage: Most of these new axons are found lying around the periphery of the tubes, some apparently in the substance of the Schwann cells. Nearly all the axons are within the tubes, however, and very few can be definitely identified outside—an observation which agrees with the findings of most workers, though Hammond and Hinsey (1945) claimed that most of the fibres grow between the tubes.

There are some axons of about 5μ in diameter which take the stain very well. These may be what Cajal (1928) called " preserved " fibres, which will eventually degenerate. Portions of degenerating small non-medullated fibres are also known to persist at least five to seven days after operation, so that not all the fine fibres can with certainty be called new. For this reason fibre counts do not give a true picture of the axon population in the early stages and none was made until the fifteenth day. At this time it is probable that undegenerated fibres no longer had any significant effect on the values found and they certainly had none thereafter.

Possibility of differentiating axons and nuclei: It is clear from *Fig.* 599 that with good staining the nuclei are fairly easily distinguished from the nerve-fibres, and although some of the latter are difficult to identify and therefore liable to be missed, a fairly accurate count is possible with care. Some empty tubes can be seen in *Fig.* 600, but the degenerate remains of the old axons and myelin sheaths are not much in evidence.

Results of Fibre Counts made 15 to 25 Days After Crushing.—For reasons already given the fifteenth day of regeneration was taken as a base line from which time axon counts could usefully be made. While regeneration is far from complete at this stage, in only one case did an examination of any part of a nerve operated upon 15 days previously fail to yield some evidence of regeneration. In this instance (rabbit 1368) sections were obtained from the most distal levels of the nerve where no axons could be demonstrated, and it was therefore possible to estimate the rate of advance of the axon tips histologically. From the data of Gutmann, Guttmann, Medawar, and Young (1942) the fastest growing axons should have grown about 40 mm., though they were only seen up to 30 mm. below the crush.

Table IV.—Numbers of Axons in the N.G.M. at Various Levels after Crushing the Nerve

Level from Crush (mm.)		Time (days)	15	15	15	19	20	25	25	27
		12				387				428
		10	328		444	388				442
		8			427	399			417	510
		6				415				496
	Above	5						387		
		4		732	420	430		375		487
		3								
		2	335	823	524	876	801		818	1140
		1						526		
		Crush	555	733	798	846		650	786	1146
		1						777		
		2	589	675	598	1015	1199		960	1143
		3								
		4	611	768	547	643	958			958
		5								
		6				518			727	1041
	Below	8		435		476	955			932
		10						611	773	1003
		12				142				827
		14		182			725			936
		16								
		18								
		20					770			
		30					882		712	
		Rabbit No.	1200	1215	1368	1419	1432	909	1866	1292

The results of fibre counts from eight nerves allowed to regenerate for 15 to 25 days after crushing are given in *Table IV* and measure the extent to which the branching process affects the number of axons present in the nerve during this time. Attention is drawn to the following points :—

1. On passing from the proximal to the distal levels of the nerve following a slow initial rise there is a sudden increase in the number of axons in every case. This increase is first seen near (i.e., just above) that level judged to be the site of the crush. The greatest number of fibres is found near this level and by 20 days is three times the normal number. Below the crush, however, there is a rapid and progressive decline in the number of fibres before the twentieth day (*see Fig.* 590). Thus the multitude of axons seen at the crush is reduced to the normal number about 10 mm. below it. From the twentieth day onwards at least twice the normal number of fibres were present throughout the distal part of the nerve (i.e., at least 30 mm. below the crush).

2. The nerve is most profoundly affected by the lesion from about 2 mm. above the crush downwards. There is no very significant increase higher

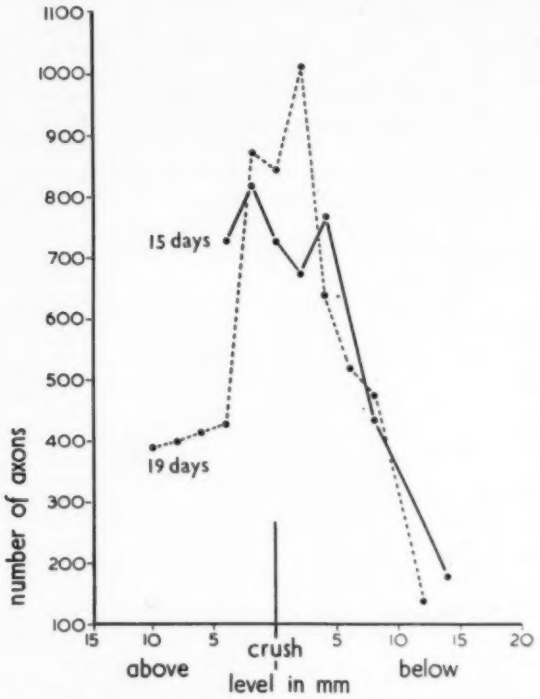

FIG. 590.—Numbers of axons at various levels along the n.g.m. 15 and 19 days after crushing the nerve.

than 6 mm. above the place where the forceps were applied. In one case only was there an appreciable increase in the number of fibres 8 mm. above the crush (rabbit 1292), and examination of *Fig.* 603

Table V.—NUMBERS OF AXONS IN THE N.G.M. AT VARIOUS LEVELS AFTER CRUSHING THE NERVE

Level from Crush (mm.)	Time (days)	35	35	35	35	50	50
Above	10					413	339
	8	478	450			405	347
	6	474	444		428	402	367
	4				512	429	365
	2	605	666		608	668	764
	Crush	941	971		903		877
	2	1000	782	1296	824	1086	808
	4				722	1120	769
	6	825	943	828	733	1002	
	8				755	948	797
Below	10	818	778		684	788	
	12		807		667	708	744
	14	775			631		
	16				611		
	18	913	577		689		802
	20		550		666		
	22						
	24		605				
	26						782
	28						
	30						
	Rabbit No.	686	1206	1168	1290	1201	1262

shows this to be due to groups of small fibres. This photograph might well be taken for a section of a normal nerve, however, and there are no obviously degenerate fibres and no empty tubes.

3. *Fig.* 601 (L/S 25-day crush 3 mm. proximal to the centre of the crushed segment of the nerve) gives a typical picture of what is seen at an early stage of regeneration. Compare this with *Fig.* 600, which is a corresponding section of a normal nerve. The tubes are packed with parallel running fibres, which are rarely observed branching, even in thick sections. Many more elongated nuclei are evident than normally. Examination of a transverse section

Table VI.—NUMBERS OF AXONS IN THE N.G.M. AT VARIOUS LEVELS AFTER CRUSHING THE NERVE

Level from Crush (mm.)	Time (days)	75	100	100	200	200	225
Above	12			416	420	392	
	10	560	351	411	440		
	8	570					
	6	549				405	358
	4	558	342	569			
	2	781	430	533		460	522
	Crush	1105	491			458	500
	2	846	605	551	649	579	489
	4	788	518	521		552	
	6	675	515			571	484
	8	699					
	10	694	489	606		553	485
	12	630					
	14				801		554
	16						
	18					498	684
	20		516	804			649
	22						
	24		518	925			627
	26						
	28			1044	817		
	30				879		
	32						
	34	667					
	Rabbit No.	1277	1273	1907	1551	1294	1543

(*Fig.* 605) taken 2 mm. proximal to a 27-day crush (rabbit 1292) shows that though there are a great many axons (1140 counted) some tubes have only axonal remains or are empty. *Figs.* 605 and 606 show the appearance of sections 2 mm. above and 10 mm. below the crush in the same nerve. It was

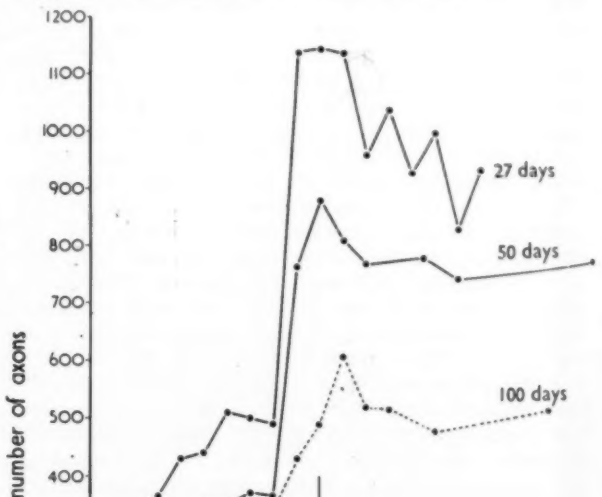

FIG. 591.—Comparison of the numbers of axons found at various levels along the n.g.m. 27, 50, and 100 days after crushing the nerve.

not possible to get sections in the more distal levels of this nerve, but *Fig.* 607 (rabbit 1866) illustrates the appearance 26 mm. below the crush at a similar stage of regeneration. It is interesting to note that

sometimes only the tubes around the peripheral part of a transverse section have several axons, while in those of the centre of the section a single axon is seen (*see Fig.* 602, 2 mm. above 20-day crsuh).

Results of Fibre Counts made 35 *and* 50 *Days after Crushing.*—These are set out in *Table V*, but differ little from those for the twentieth and twenty-fifth after operation. Above the crush the nerve is already normal by 100 days, both as regards the number of axons and its appearance (*see Fig.* 591). Below the lesion, although sections appear approximately normal (*see Fig.* 610) counts show nearly 50 per cent more fibres 200 days after crushing. *Fig.* 592, for example, shows 553 axons 10 mm.

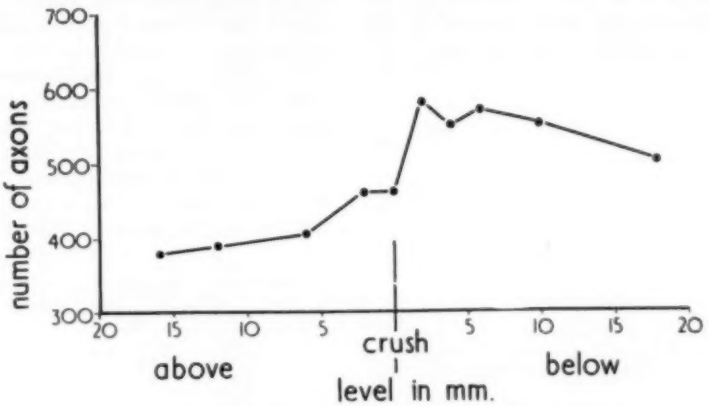

FIG. 592.—Numbers of axons at various levels along a n.g.m. crushed 200 days previously.

days, though there are rather fewer (17 per cent) axons above the crush than formerly. This marks the beginning of a process by which most of the new fibres are eliminated. *Fig.* 608 is taken from a section 2 mm. above a 50-day crush (rabbit 1201) and shows one tube with eight fibres arranged around its periphery, but most have only one. There also appear to be far fewer nuclei at 50 days. Abercrombie and Johnson (1946) found that the nuclear population of a degenerating peripheral nerve reaches a peak at 25 days. Thomas (1948) confirmed this for the n.g.m., and his figures for this nerve show a marked reduction by 50 days. The greatest number of fibres now occurs below the lesion (*Fig.* 609, 10 mm. distal to 50-day crush), and the number is nearly constant and still about twice the normal throughout the distal region.

The late Stages of Regeneration, i.e., from 75–225 *Days.*—(Fibre counts made during this period are given in *Table VI.*)

Many of the new axons now disappear and the nerve returns to something like its original state, though it does not quite reach this even 225 days below the crush, compared with the normal number of 392.

It is to be noted that in those nerves where sections were obtained near the entry of the nerve to the muscle there is a secondary rise in the number of fibres, presumably due to the branching normally found at this level (*see* Evans and Vizoso, 1951 and *Table II*).

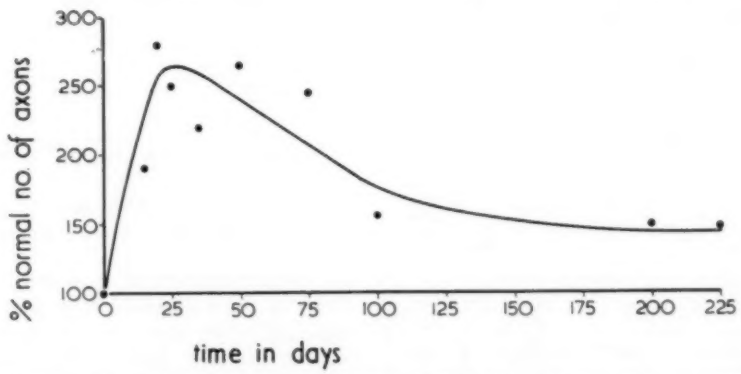

FIG. 593.—The number of axons found in the crushed region of the n.g.m. at various times after operation expressed as a percentage of the normal number.

The Different Stages of Regeneration Compared.—For a fair comparison of axon counts made from different nerves allowance must be made for the normal variation in their fibre content. *Table VII* gives the counts of the number of axons expressed as a percentage of the normal number of fibres: (1) In the region of the crush where the greatest number is found; (2) 10 mm. below the crush.

These figures are calculated on the basis of taking the number of fibres counted 10 mm. proximal to the lesion as being the normal. Where no counts could be made at this level, 400 was assumed to be the normal number (450 in the case of rabbit 1277). *Figs.* 593, 594 are graphs based on the figures in this table; they show:—

1. *At the Crush* (*Fig.* 593).—

a. The branching of the regenerating fibres in a crushed nerve proceeds rapidly within the first 20 days.

b. Each parent fibre gives rise to three others by this time, on the average.

c. Between 20 days and 50 days this number of branches is maintained.

d. There is a comparatively slow decline in the number of branches during the next 50 days.

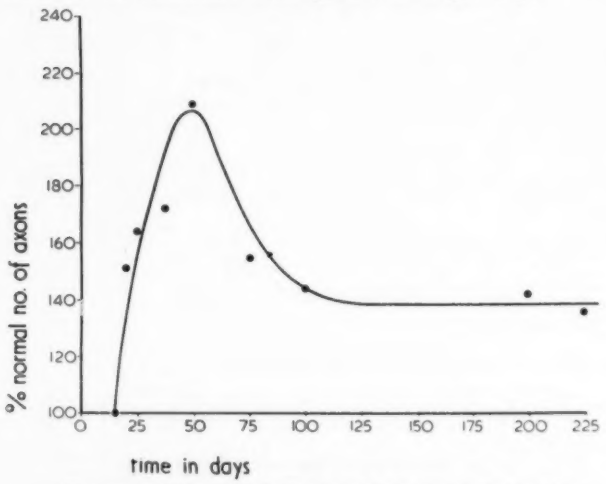

FIG. 594.—The number of axons found 10 mm. below the crushed region of the n.g.m. at various times after operation expressed as a percentage of the normal number.

e. From 100 days to 225 days the number of branches remains unchanged and some of the original parent fibres must still give rise to branches

Table VII.—REGENERATION FOLLOWING CRUSHING N.G.M.
(PER CENT NORMAL NUMBER OF FIBRES)

Rabbit No.	*Time* (days)	*Crush*	*Mean at Crush*	*10 mm. below Crush*	*Mean 10 mm. below Crush*
1215	15	206		100	
1368	15	180	191	—	
1200	15	186		—	
1419	20	262		82	
1432	20	300	281	220	151
909	25	201		158	
1292	25	259	250	150	164
1866	25	290		183	
686	35	209		171	
1200	35	216	217	173	172
1290	35	226		171	
1201	50	271		191	
1262	50	259	265	227	209
1277	75	246	246	154	154
1273	100	173	156	139	143
1907	100	138		147	
1294	200	148	148	141	141
1543	225	146	146	135	135

since 50 per cent more axons are found than in the normal nerve.

2. 10 *mm. below the Crush* (*Fig.* 594).—

a. 10 mm. below a crush the number of axons increases with time so that after 15 days have elapsed the nerve has regained its normal complement of fibres.

b. By 50 days twice the normal number of fibres is found, which is the maximum number at any time at this level. Therefore of the branches formed in the region of the crush about one-third fail to grow 10 mm. towards the periphery.

c. There is a reduction in fibre numbers during the next 50 days.

d. From 100 days to 225 days the number of axons remains constant (about 40 per cent more than normal) and of every three axons present at 50 days only two persist.

Myelination of fibres after crushing the n.g.m.: *Table VIII* gives the results of counts of medullated fibres made from material stained by the Weigert-Pal technique. Comparing the counts made at 25 days with those made on Bodian-stained material it is clear that only a proportion of the new axons formed near the lesion become myelinated at this stage. This is what would be expected as the new fibres slowly acquire medullated sheaths and only begin to do so about the tenth day (Hentowa, 1933). The results of the present investigation also fit in with

Table VIII.—NUMBERS OF MEDULLATED FIBRES IN THE N.G.M. AFTER CRUSHING THE NERVE

Level from Crush (mm.)	Time (days)	25	30	40	50	60	100
Above	12						362
	10				422		
	8			454			367
	6					403	
	4		343	453	418	410	
				444		409	
	2	421	322	596	414		371
				1019		364	
	Crush	664	619		501	660	411
Below	2	746	256	999	534	514	471
	4				498	441	
	6			675			
	8	269	169			456	
	10			598	431	467	
	12						
	14			543			
	16						
	18					601	
	20	173			516	578	440
	30						496
	Rabbit	1257	3021	601	3026	746	1365

the view that medullation proceeds centrifugally and follows the advancing axon tips down the nerve.

Below the crush new medullated fibres could be seen at least 18 mm. in a distal direction as early as 20 days, but most of the axons found in the distal levels of the Bodian-stained preparations remain unmyelinated. In fact, less than half the total number of fibres are represented in the Weigert sections 8 mm. below the lesion at 30 days. *Figs.* 611, 612, 613 illustrate what is happening at this stage of myelination. The first photograph is taken 4 mm. above the crush, which has not visibly affected the nerve at this level. A few degenerate fibres were seen in the section from which this was taken, but the number of fibres (343) is within normal limits. The second photograph from a section through the crushed region shows many new, mostly thinly myelinated small fibres; 619 of these were counted. A great deal of myelin debris is seen and a few large degenerate fibres were noted. In the third photograph, 8 mm. below the lesion, many tubes devoid of medullated fibres are seen. Compare this with the appearance of the axons at a slightly earlier stage of regeneration (27 days) in *Fig.* 606 where most tubes have several axons. Only 169 new fibres were counted at this level.

By 40 days 1019 medullated fibres were noted in the vicinity of the lesion—the normal number for this nerve is 454. However, to judge by the degree of swelling around the crush in this case, the nerve

Table IX.—Numbers of Axons in the N.G.M. after Primary Suture of the Nerve

Level from Suture (mm.)	Time (days)	15	15	20	25	25	35	35
Above	12							
	10		388				402	499
	8				375	361	423	
	6				387		469	
	4	602	432		419	661	705	654
	2	1163	541	599	576	981	1368	1103
	Suture			1374				
	2	407	660	891	1009	690	1096	1000
	4		304			641	1609	
	6			943			1433	830
	8						1369	1080
Below	10		53		1065	479	1224	1078
	12			578			1237	
	14							
	16							
	18							898
	20				679	180		
	Rabbit No.	1250	2080	1235	1236	1604	1216	1529

was probably subjected to more trauma than usual at operation. The illustration of the crushed region of this nerve (*Fig.* 618) shows rather more fibrous

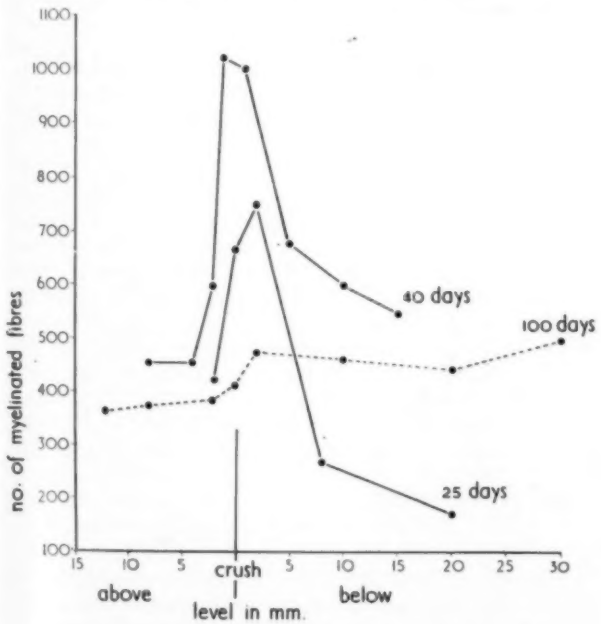

Fig. 595.—The numbers of myelinated fibres at various levels along the n.g.m. 25, 40, and 100 days after crushing the nerve.

tissue than usual in the intervals between the fibres. The increase in their number is seen to be due to groups of 'daughter' fibres surrounding some of the larger ones. 15 mm. below the crush 543 fibres were recorded (*Fig.* 595), but this falls short of the number of axons present. Moreover there is no rise in the number of myelinated fibres with the course of time (*Fig.* 596). It appears, therefore, that about half the axons formed in the early stages remain permanently unmyelinated.

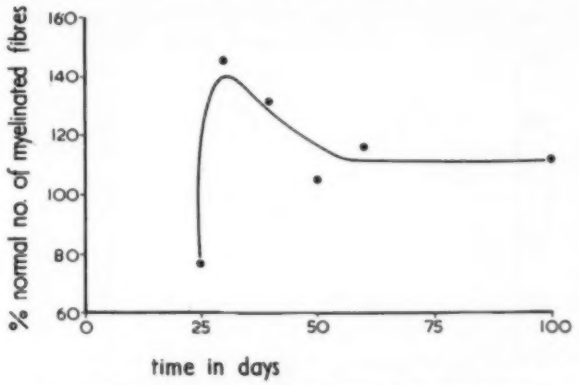

Fig. 596.—The numbers of myelinated fibres found 10 mm. below the crushed region of the n.g.m. at various times after operation expressed as a percentage of the normal number.

By 100 days (*Fig.* 595) the nerve appears normal at all levels (*see Figs.* 615–617 taken 8 mm. above the crush, through the crush, and 10 mm. below it, respectively). The fibres are smaller and more thinly myelinated in the distal levels, but the number does not vary much. Comparison of *Figs.* 596 and 594 shows that the numbers of medullated fibres and axons now nearly coincide, 80 per cent of the total being myelinated. Davenport and others (1939)

Table X.—Numbers of Axons in the N.G.M. after Primary Suture of the Nerve

Level from Suture (mm.)	Time (days)	35	50	50	111	200	225	225
Above	12		414	402				
	10		650	409	339	403	305	
	8							
	6						339	
	4	617						971
	2	944	1822	1585	480	1243	531	989
	Suture							
	2	1120			533	1468	570	
	4	1324	1012	1325				1090
	6	1135					640	
	8	1108						
	10	945	920		566	800	609	1111
	12	911		1029				
	14	950					725	
	16							
	18							
Below	20		839		511	796		872
	22					769	734	
	24			1196				
	26							
	28			1392				
	30					746		
	32				546			
	40				572			
	Rabbit No.	1228	1464	1991	2157	1251	1525	1520

found only 64 per cent of the medullated fibres initially present in the sciatic at a 100 days, though about twice that number were counted in the n.g.m. The proportion of sensory fibres in the sciatic nerve must greatly exceed that in the n.g.m., however, so there is some reason to think that motor fibres

have their medullary sheaths restored at a quicker rate than sensory fibres.

Suture of the Nerve to the Medial Head of the Gastrocnemius.—By the tenth day of regeneration a great many small well-stained axons were noted 2 mm. above the lesion, and in one case many were

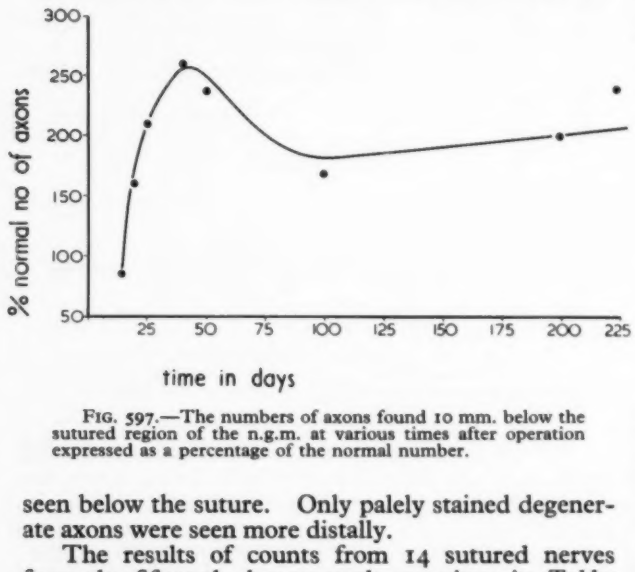

FIG. 597.—The numbers of axons found 10 mm. below the sutured region of the n.g.m. at various times after operation expressed as a percentage of the normal number.

seen below the suture. Only palely stained degenerate axons were seen more distally.

The results of counts from 14 sutured nerves from the fifteenth day onwards are given in *Tables IX* and *X* and *Fig.* 597. They are similar to those for crushed nerves, but the following differences should be noted :—

1. The maximum number of branches was greater than in the case of crushed nerves. An average of 4½ branches were formed by the regenerating fibres in one case (rabbit 1464). The number

Table XI.—NUMBERS OF AXONS IN THE SURAL NERVE AT VARIOUS TIMES AFTER CRUSHING THE NERVE

Level from Crush (mm.)	Time (days)	15	25	35	150	250
Above	20	1527		1922		
	10	1556	1667			
	2	1879	1425		2138	1893
Crush			2243			
Below	2		1547		2717	2217
	4		1239	2755		
	10	1316			2730	2361
	20		1175	2517		
	30		1055		3048	
	40					
	50					1954
	Rabbit No.	2209	2264	2274	1666	1547

of axons in the sutured region varied from 157 per cent to 440 per cent of the estimated normal number.

2. The greatest number of axons was frequently seen just above the lesion. This is probably due to some of the fibres taking a recurrent course. *Fig.* 619 shows some fibres running transversely 2 mm. above a 50-day suture (rabbit 1464).

3. The figures 10 mm. below the suture consistently reach a maximum value about 35 to 50 days. Before 20 days far fewer axons were noted at this level than in the case of crushed nerves (i.e., 53 instead of 435).

4. Each parent fibre still has about 3 branches at 200 days near the suture, and 2 of these extend 10 mm. or more beyond the suture.

Sural Nerve Crushes.—Regenerating sensory fibres were studied by means of experiments made on the sural nerve. The findings were very different from those already noted for a motor nerve the (n.g.m.) and are set out in *Table XI.* The following differences should be noted :

1. For the first 25 days after crushing a sural nerve the number of fibres below the lesion is less

Table XII.—NUMBERS OF AXONS IN THE PHRENIC NERVE 25 AND 35 DAYS AFTER CRUSHING THE NERVE

Level from Crush (mm.)	Time (days)	25	35
Above:	6		774
	5	885	
	2		792
	1	1080	
Crush			1097
Below	1	1497	
	2		912
	8		948
	10	1375	
	15	1422	
	Rabbit No.	1565	1561

than above. *Figs.* 620 and 623 (2 mm. above and 4 mm. below a 35-day crush respectively) show this. All the counts made from the distal levels are less than the normal value for this nerve (1667). The difference between the sural nerve and the n.g.m. is well brought out by Weigert preparations. Whereas there are many small fibres around one large fibre in many of the tubes of a n.g.m. which has regenerated for 40 days (*Fig.* 618), the sural nerve at the same stage has no tubes with more than one fibre (*Fig.* 614).

Table XIII.—NUMBERS OF AXONS IN THE N.G.M. AT VARIOUS TIMES AFTER CRUSHING THE NERVE AND SEVERING IT FROM ITS MUSCLE

Level from Crush (mm.)	Time (days)	25	53	53
Above	10			330
	8			
	6	390		
	4			
	2	426	520	373
Crush		713		
Below	2	925	1432	969
	4			
	6			
	8			937
	10	788	1904	
	12			1578
	14			
	16			
	18	881	2886	
	20			
	22			
	24			
	26	857		
	Rabbit No.	2295	2298	2287

2. By 35 days the number of fibres in the distal levels has reached a peak and represents a 37 per cent increase on the original figure. This means that about 20 per cent of the fibres had formed branches since there was no evidence that many of the fibres above the crush had degenerated. It is interesting to note that approximately the same proportion (20 per cent) of large medullated fibres are found in the nerve normally.

Phrenic Nerve.—*Table XII* gives the results obtained for the phrenic nerve. Regeneration in this nerve is similar to that in the n.g.m., but fewer

axons were counted at the crush (169 per cent of the number found above the crush at 25 days against 250 per cent for the n.g.m.). Both nerves are motor (i.e., muscle) nerves, the difference may be accounted for by the fact that the n.g.m. contains larger fibres than the phrenic nerve.

Effect of Severance of Nerve from its Muscle.—The early stages of regeneration following crushing of the n.g.m. isolated from its muscle have been investigated and the results are given in *Table XIII*.

1. For the first 25 days the nerve behaves as if it had been merely crushed, to judge by the number of fibres it contains.

2. By 53 days the great increase in the number of fibres found by Aitken, Sharman, and Young (1947) under these conditions is evident. *Fig.* 621 shows each tube crowded with axons.

3. Disregarding the vast number of fibres near the neuroma (this has been shown by Aitken (1949) to be due to many taking a recurrent course) the counts of axons 10 mm. distal to the crush are still about five times the estimated normal number at 53 days.

DISCUSSION

The results presented confirm that an axon gives rise to several sprouts after interruption, but the number of branches produced by all the fibres in the nerve-trunk is far smaller than was estimated by the early workers in this field (Perroncito, Cajal, Ranson, and others). These authors based their findings on the examination of the branches formed by individual fibres. In the regenerating n.g.m. each axon has an average of three branches at the site of a crush, but some fibres may well give rise to many more (up to 25 axons were counted in a few tubes) while others fail to regenerate at all.

It is possible that the type of fibre determines the number of branches formed. Few fibres are found below a lesion of the sural nerve. This is also true of other nerves containing large numbers of sensory fibres (Davenport, Chor, and Dolkart, 1937, and Gutmann and Sanders, 1943). The comparative inability of the sural nerve-fibres to form branches may therefore be connected with the sensory nature of the nerve. Against this is the fact that about half the axons in the n.g.m. are afferent (Eccles and Sherrington, 1930). Of the nerves used in this work the n.g.m. has the largest and the sural nerve the smallest fibres, while the fibres of the phrenic nerve are intermediate in size, though approximating more nearly to those of the n.g.m. The results for these nerves shown in *Fig.* 598 could be explained if the number of branches depends on fibre size. During this investigation only the large tubes were found to contain many fibres. This is evidence that large fibres form more branches than smaller fibres.

During regeneration of the n.g.m. all the tubes become re-innervated, although each fibre only forms three sprouts. This argues for other factors than central ones controlling regeneration. Indeed it is known that peripheral influences have a powerful effect on regenerating nerve-fibres, leading to a reduction in their number (Weiss and Taylor, 1944; Sanders and Young, 1944, 1945; Aitken, Sharman, and Young, 1947; and Aitken, 1949). When the n.g.m. is crushed proximally but severed from its muscle distally, the effect of the lack of the normal peripheral influence is evident by 53 days. More than twice the number of fibres which would have been formed following a simple crush has been noted under these circumstances. The temporary absence of the peripheral influence in sutured nerves may be one reason why their nerve-fibres branch more often.

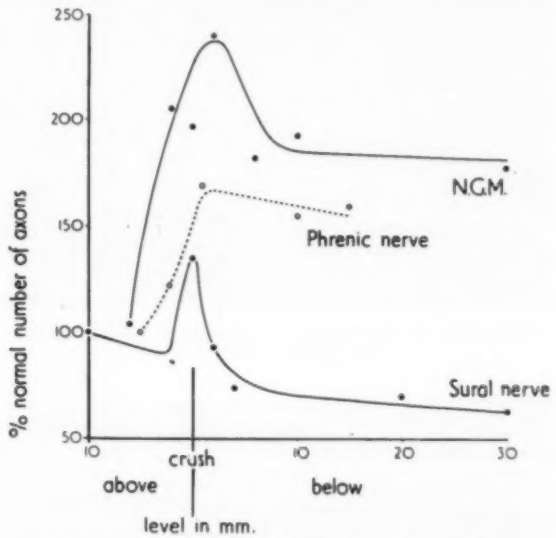

FIG. 598.—Comparison of the numbers of axons found at various levels along the n.g.m., phrenic nerve, and sural nerve 25 days after crushing expressed as a percentage of the normal number for each nerve.

Fate of the Branches formed during Regeneration.—The earliest branches to appear are abortive and degenerate by the third day (Ranson, 1912) though a few persist for 25 days or more (Perroncito, 1906). Relatively permanent branches are not numerous until the tenth day. Between 50 and 100 days after crushing the nerve the majority of the new branches in the n.g.m. disappear, but from then onwards, as far as the process has been followed in this work (up to 225 days), no further change in the number of branches occurs. Why so many axons fail to survive is not clear. It may be due to purely mechanical factors, some of the fibres in the crowded tubes undergoing a kind of pressure atrophy. Again, the cell body may be unable to maintain an adequate supply of nutrient to more than one or two branches. Possibly only those fibres making contact with the periphery are capable of surviving, and the fact that many of the new axons do not become myelinated may also have some bearing on their fate.

The mechanism by which the axons are removed needs further elucidation, especially as few degenerating fibres are observed from the fiftieth to the hundredth day when the axon population is diminishing. The fluid properties of axoplasm (shown by Young, 1935, 1936) and other workers may, however, result in the fusion of some adjacent fibres and so reduce their number.

It is generally assumed that the elicitation of Tinel's sign in a regenerating nerve is dependent

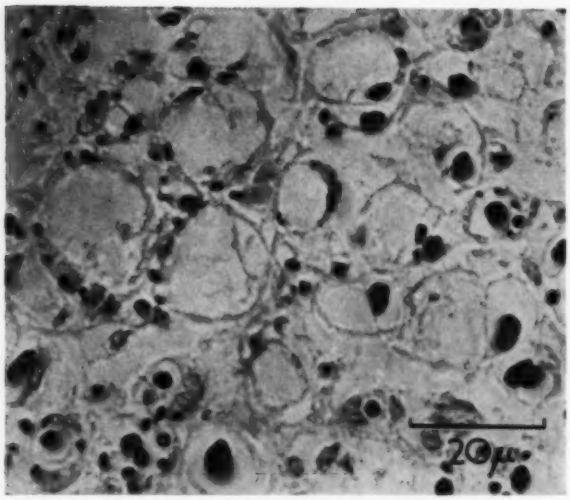

FIG. 599.—T/S crushed region n.g.m. at 10 days. Rabbit 2159. Bodian stain.

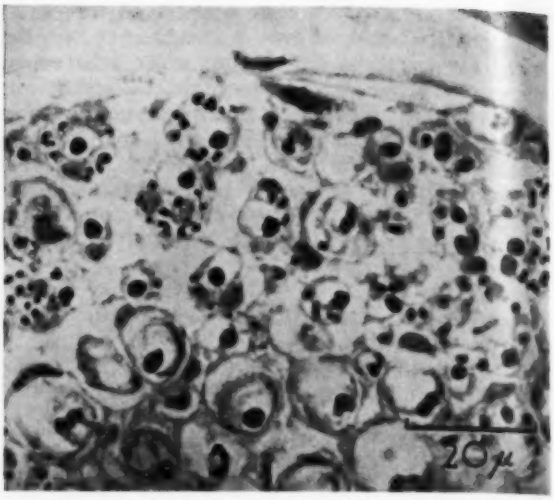

FIG. 602.—T/S n.g.m. 2 mm. above crush at 20 days showing peripheral part of section containing small fibres. Rabbit 1432. Bodian stain.

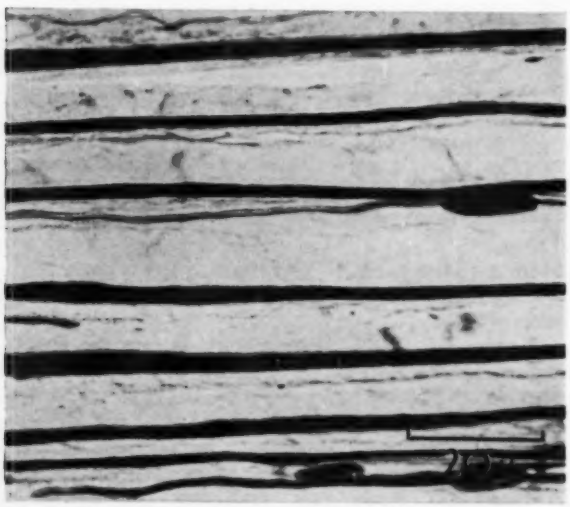

FIG. 600.—L/S normal n.g.m. Rabbit 2111. Bodian stain.

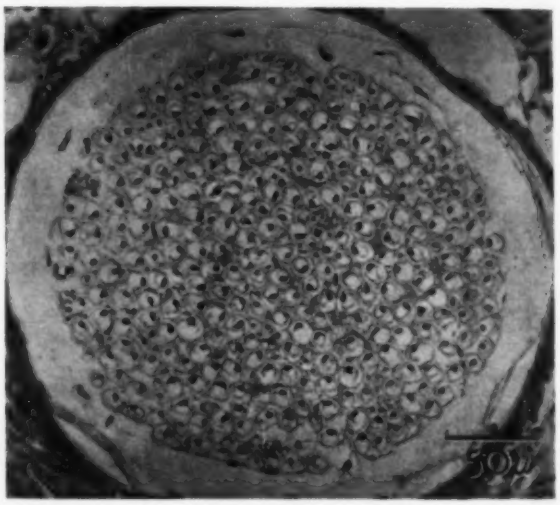

FIG. 603.—T/S n.g.m. 8 mm. above crush at 27 days. Rabbit 1292. Bodian stain.

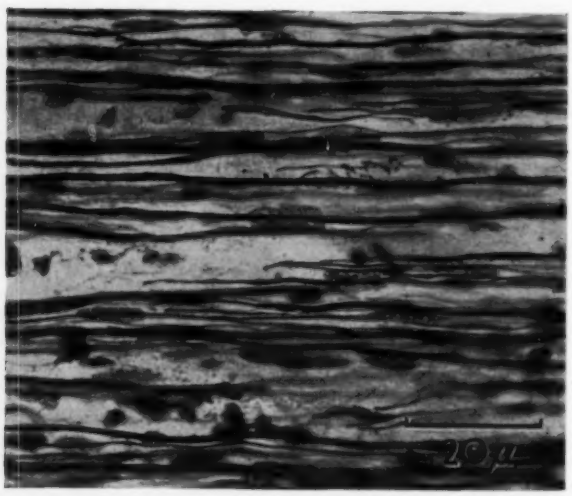

FIG. 601.—L/S n.g.m. taken 3 mm. proximal to the centre of the crushed segment of the nerve at 25 days Rabbit 2115. Bodian stain.

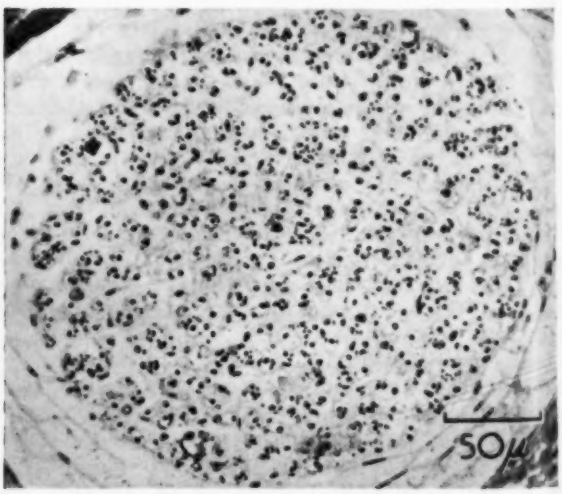

FIG. 604.—T/S n.g.m. 2 mm. above crush at 27 days from same nerve as *Fig.* 605. Rabbit 1292. Bodian stain.

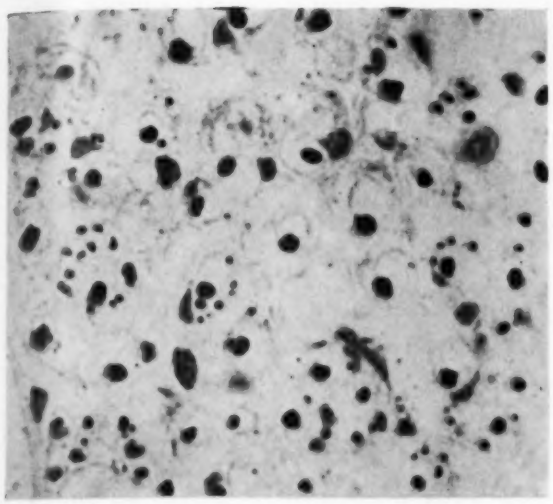

FIG. 605.—T/S n.g.m. 2 mm. above crush at 27 days (High-power view of *Fig.* 606). Rabbit 1292. Bodian stain.

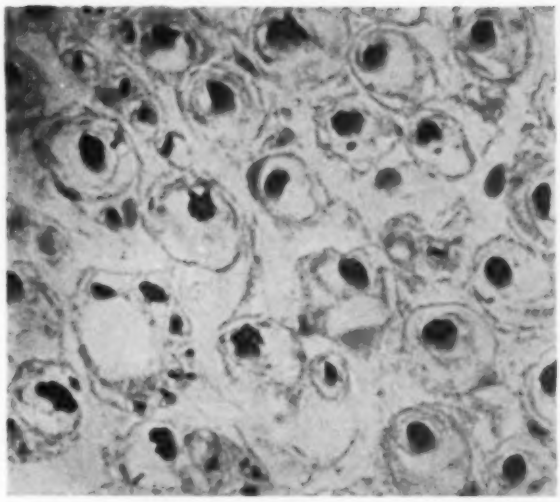

FIG. 608.—T/S n.g.m. 2 mm. above crush at 50 days. Rabbit 1201. Bodian stain.

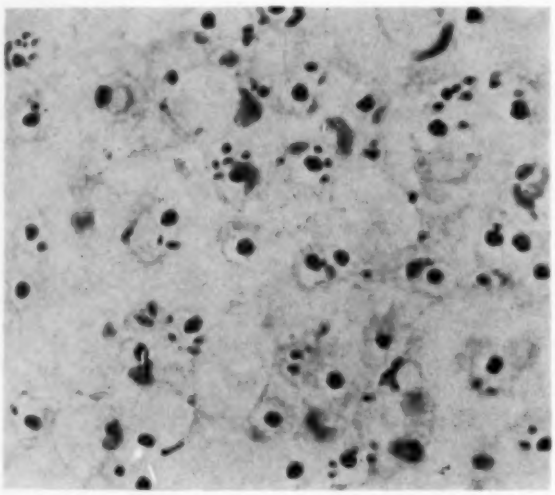

FIG. 606.—T/S n.g.m. 10 mm. below crush at 27 days (from same nerve as *Fig.* 604, 605). Rabbit 1292. Bodian stain.

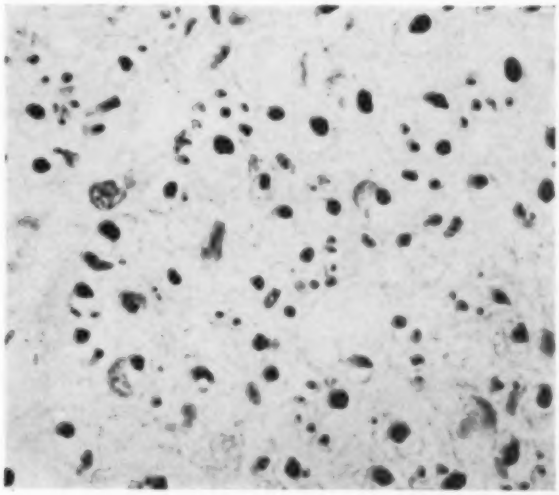

FIG. 609.—T/S n.g.m. 10 mm. below crush at 50 days. Rabbit. 1262. Bodian stain.

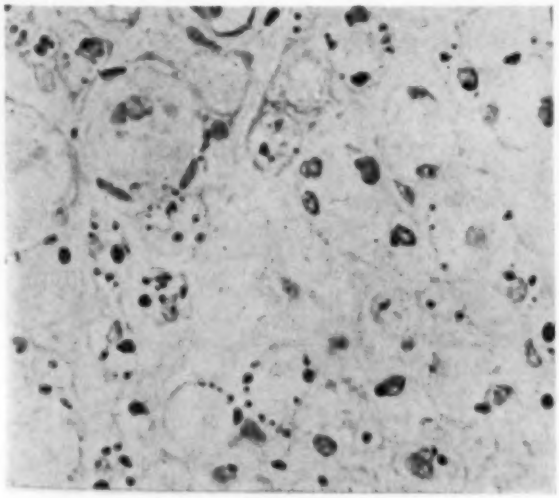

FIG. 607.—T/S n.g.m. 26 mm. below crush at 25 days. Rabbit 1866. Bodian stain.

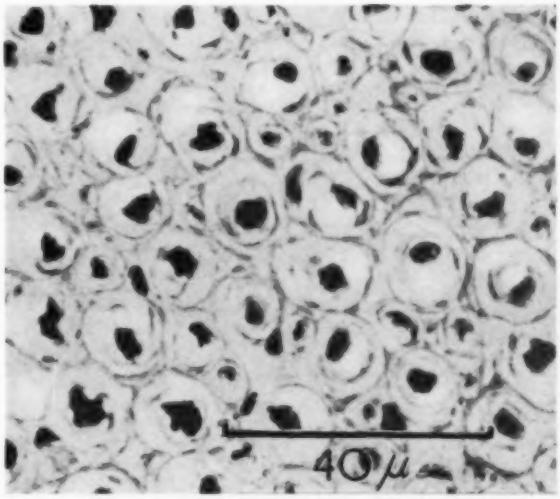

FIG. 610.—T/S n.g.m. 10 mm. below crush at 200 days. Rabbit 1294. Bodian stain.

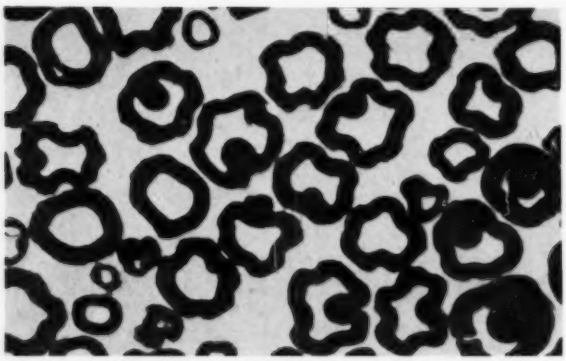

FIG. 611.—T/S n.g.m. 4 mm. above crush at 30 days. Rabbit 3021. Weigert-Pal stain.

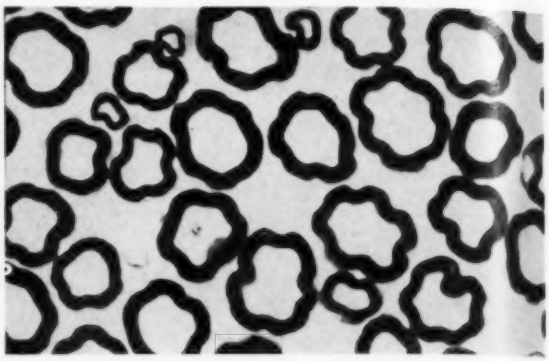

FIG. 615.—T/S n.g.m. 8 mm. above crush at 100 days. Rabbit 1365. Weigert-Pal stain.

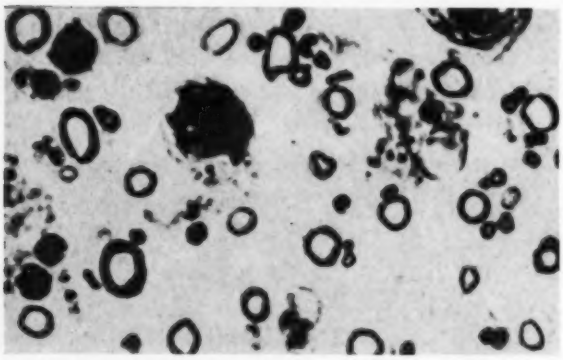

FIG. 612.—T/S crushed region n.g.m. at 30 days. Rabbit 3021. Weigert-Pal stain.

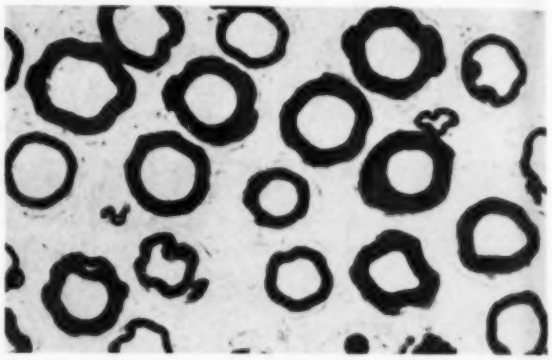

FIG. 616.—T/S crushed region n.g.m. at 100 days. Rabbit 1365. Weigert-Pal stain.

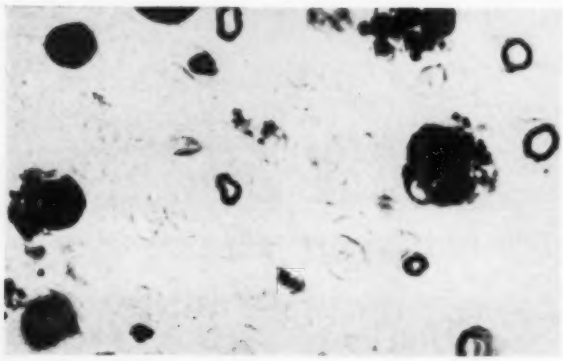

FIG. 613.—T/S n.g.m. 8 mm. below crush at 30 days. Rabbit 3021. Weigert-Pal stain.

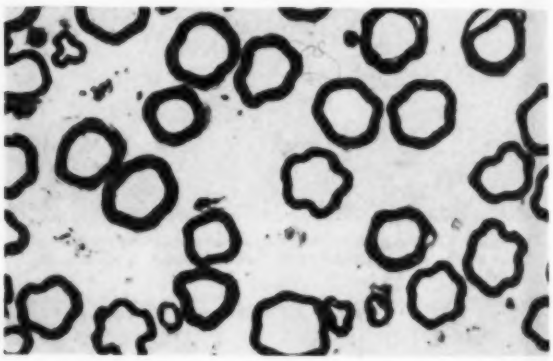

FIG. 617.—T/S n.g.m. 10 mm. below crush at 100 days. Rabbit 1365. Weigert-Pal stain.

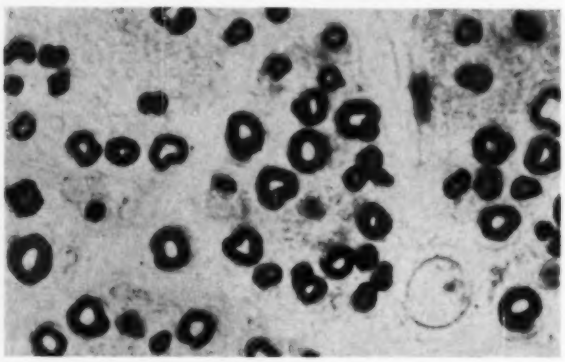

FIG. 614.—T/S crushed region sural nerve at 40 days. Weigert-Pal stain.

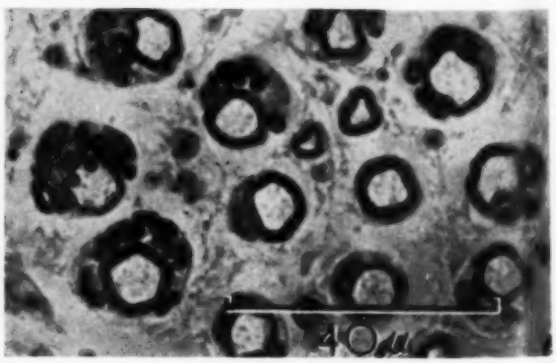

FIG 618.—T/S crushed region n.g.m. at 40 days. Rabbit 601. Weigert-Pal stain.

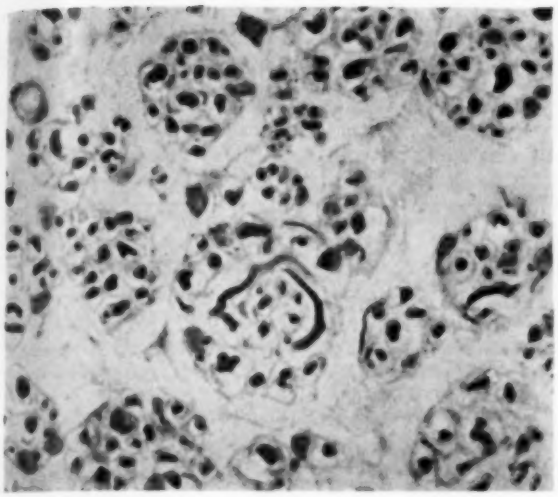

FIG. 619.—T/S n.g.m. 2 mm. above suture at 50 days. Rabbit 1464. Bodian stain.

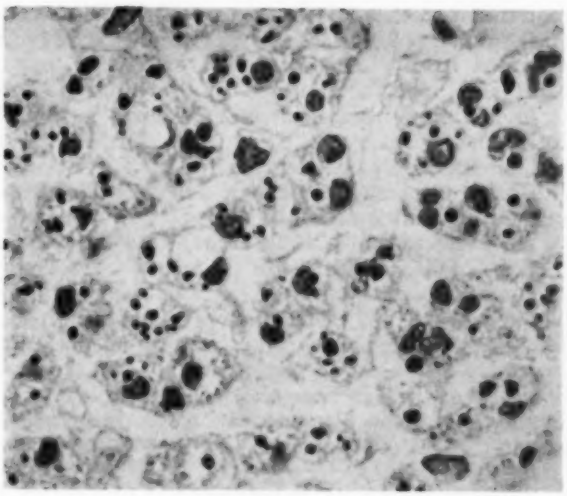

FIG. 622.—T/S n.g.m. 10 mm. below suture at 50 days. Rabbit 1464. Bodian stain.

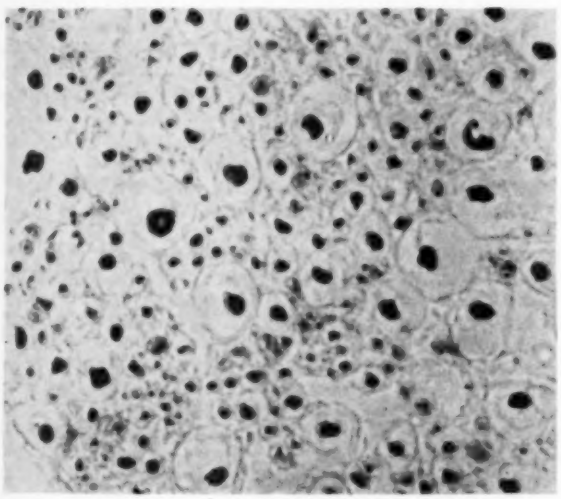

FIG. 620.—T/S sural nerve 2 mm. above crush at 25 days. Rabbit 2264. Bodian stain.

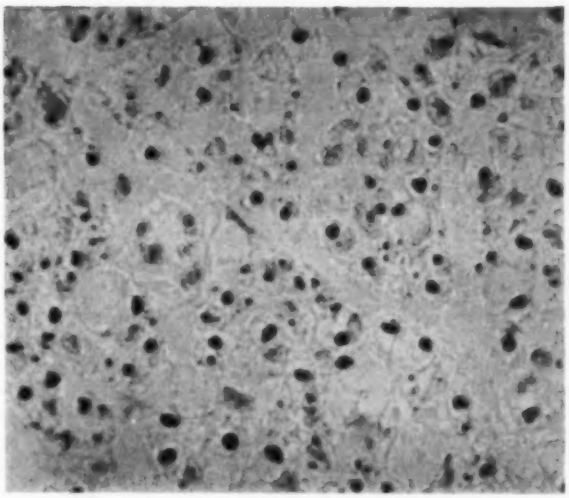

FIG. 623.—T/S sural nerve 4 mm. below crush at 25 days. Rabbit 2264. Bodian stain.

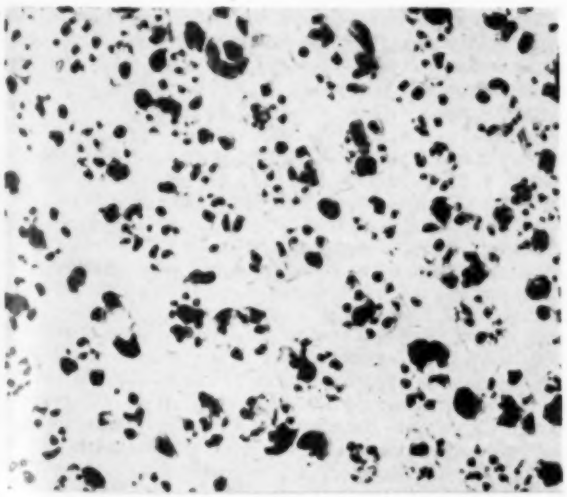

FIG. 621.—T/S n.g.m. (regenerating without connexion to muscle) taken 16 mm. below crush at 53 days. Rabbit 2298. Bodian stain.

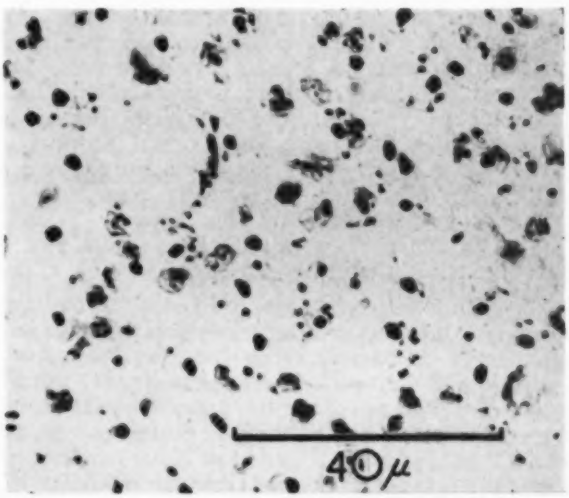

FIG. 624.—T/S n.g.m. (regenerating without connexion to muscle) at 25 days. Rabbit 2295. Bodian stain.

upon the presence of small non-myelinated axons. The number of these at any given time may be estimated from a comparison of the figures for the axons and medullated fibres in the tables for the n.g.m. The number of medullated fibres is progressively smaller on passing from the crushed region to the distal levels of the nerve for the first 40 days. This fact supports the view held by some previous workers (Howell and Huber, 1892 ; Kirk and Lewis, 1917 ; Sanders and Young, 1942) that the process of medullation spreads down the nerve. Davenport Chor, and Cleveland (1939) came to the conclusion that growth of the axons and myelination proceed almost simultaneously, but the results presented here show that a time lag of about 10 days separates these two processes near the lesion, as claimed by Hentowa (1933). Peripherally the time lag is greater (i.e., about 20 days).

CONCLUSIONS

1. On the average each axon central to a crushed point in a motor nerve of the rabbit gives three branches by 20 days. The level at which branching begins is about 6 mm. above the injury. Below the crush the number of fibres reaches its maximum later (at 50 days). By 100 days many branches, both at the crush and peripherally, have disappeared and presumably degenerated. The fibre content of the nerve is then about 50 per cent higher than normal and remained so for as long as it was studied (225 days).

2. Medullation of the regenerating nerve-fibres proceeds from about 10 days until 40 days, when the number of myelinated fibres reaches a peak. About half the axons formed in the early stages never become medullated and disappear. By 100 days of regeneration, because many unmyelinated fibres have disappeared, the myelinated fibres account for by far the greater part of the total and are present in almost the normal proportion.

3. Non-medullated fibres have been demonstrated in the normal nervus gastrocnemius medialis. The ratio of myelinated to non-myelinated fibres in this nerve is 1 : 0·3.

4. In nerves that have been severed and sutured immediately branching is greater in extent than after crushing. On the average each original axon can form as many as four to five branches. The degree of branching is more variable than after a simple crush. Furthermore the distal portion of the nerve contains twice the normal number of fibres even 200 days after the lesion, in contrast to crushed nerves, which have nearly returned to a normal axon population by this time.

5. The fibres of a muscle nerve give rise to more branches than the sensory fibres of a skin nerve during regeneration. Some evidence has been obtained that this is because muscle nerve-fibres are larger.

I am much indebted to Professor J. Z. Young for his constant advice, encouragement, and criticism, and also to the late Mr. F. J. Pittock and to Mr. J. Armstrong for technical help.

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RESECTION FOR CARCINOMA OF HEAD OF PANCREAS

TWO 5-YEAR SURVIVALS

By E. G. MUIR, London

Since Whipple's description in 1935 (Whipple, Parsons, and Mullins), the operation of pancreatico-duodenal resection has been widely used for carcinoma in the head of the pancreas, whether arising in the ampulla, terminal common bile-duct, or pancreas itself. Enthusiasm for the operation has been somewhat tempered by poor after-results and there are some who feel that it is seldom justified. It is certainly true that 5-year survivals are rare and, though they have occurred, none has so far been recorded in this country. Two such cases are here described and an attempt made to evaluate the operation.

CASE REPORTS

Case 1.—C. F., a man of 60, was admitted to hospital on Aug. 20, 1949, with a history of many years indigestion and a diagnosis of chronic duodenal ulcer with duodenal deformity which had failed to respond to medical treatment. He had never been jaundiced. Laparotomy on Aug. 24, showed a mass the size of an orange in the head of the pancreas involving the first and second parts of the duodenum. There were no secondaries, the head of the pancreas was quite mobile and the tumour appeared localized. The head of the pancreas, together with the pyloric antrum and duodenum, was resected and the oversewn neck of the pancreas implanted into the first loop of the jejunum between the common bile-duct and the divided end of the stomach. Recovery was uneventful. Histology showed the growth to be a 'colloid' or mucinous adenocarcinoma of the pancreas. There were no glandular secondaries and the common bile-duct, though in contact with growth, had not been compressed. The patient was discharged on a reduced-fat diet and pancreatin. Over the next two years he attended the hospital from time to time. He remained in fair health, but failed to gain weight, and there was evidence of a marked failure of fat absorption with loose pale stools. In May, 1952, he developed symptoms suggestive of mild obstruction, and a laparotomy showed an intussusception of the transverse colon caused by a small carcinoma. The growth was resected. No evidence of secondaries was found and the anastomoses of the previous operation appeared to be in good order. The patient made a good recovery. He continued to attend hospital from time to time, particularly when his loose stools became troublesome. On several occasions he was admitted for a few days and usually improved rapidly on a reduced-fat diet and adequate proteins. On the last occasion a barium meal suggested compression of the stomach and on June 21, 1954, a small laparotomy incision was made. This showed no evidence of secondaries from either of his carcinomas and the appearance of the stomach on the barium meal was due to its position behind the transverse colon. At the present time, 5 years after the resection for a carcinoma of the head of the pancreas and 2 years after the resection for a carcinoma of the colon, this patient is free from recurrence. He is an elderly bachelor, living in lodgings, and his straitened circumstances make an ideal diet sometimes difficult to obtain, but nevertheless his pancreatic insufficiency does not stop him from enjoying his life.

Case 2.—W. P., a man of 58, was admitted to hospital in December, 1947, with a four weeks history of jaundice. He was otherwise in good health. Laparotomy showed a small growth at the ampulla of Vater. There were no secondaries and resection of the head of the pancreas and the duodenal loop was performed. The oversewn neck of the pancreas was implanted into the first jejunal loop between the common bile-duct and the divided end of the stomach. Recovery was uneventful. Histology showed that the growth, some 3 mm. in diameter, was a papillary adenocarcinoma of the ampulla of Vater. The patient made an uneventful recovery. He regained his normal weight, there was no diarrhœa, and there was little evidence of fat wastage in his stools. Nine months after his operation he developed intermittent jaundice. Laparotomy was performed and this showed that his gall-bladder, which had previously appeared healthy, now contained gall-stones. There was no evidence of secondaries. The gall-bladder was removed, the common bile-duct explored, and some biliary debris and a small piece of silk suture removed from the region of the anastomosis to the jejunal loop. The patient made a good recovery and remains in good health. He earned his living as a coal-man and up till two years ago was still able to carry sacks of coal on his back. Now, 7 years after pancreatic resection, and 6 years after the subsequent cholecystectomy, he appears in good health and free from recurrence.

COMMENT

One of these patients had the largest carcinoma of the pancreas I have ever been able to resect: the other had the smallest. They both underwent the same operative procedure but, while one has always shown evidence of pancreatic insufficiency, the other has remained on a normal diet, without weight loss, without pancreatin, without diarrhœa, and with little evidence of fat wastage. Both have undergone major operations at intervals after the pancreatic resection.

DISCUSSION

Whipple (1951), in an editorial review, stated that until earlier operation was possible "the cures with radical surgery in ampullary growths will remain few and in cancer of the pancreas will continue to be palliative". Brunschwig (1952) later reported 3 patients alive and well 8½, 7, and over 5 years after pancreatico-duodenectomy, and Orr (1952) stated that there were then 17 cases which had lived 5–10 years after the operation. Child, Holswade, McClure, Gore, and O'Neil (1952), in an extensive review of some 150 cases submitted to resection, found only 3 known 5-year survivors and only 9 alive over eighteen months. The average survival period after radical resection was only 9 months, but in 1148 cases treated palliatively it was only 5 months. The largest personal series is that of Cattell and Warren (1953), who stressed, as did Whipple and others, the difference—both in operative mortality and post-operative prognosis—between carcinoma of the pancreas itself and that of the ampulla of Vater. The resection operative mortality was 13·6 per cent. Of 38 survivors of resection for carcinoma of the pancreas only 2 (5 per cent) survived 5 years or more: of 28 survivors of ampullary carcinoma 3 (11 per

cent) were alive and well 9 years after operation, and 11 (40 per cent) lived 3 years or more. Thirty-two cases were available for a 5-year follow-up, and this showed an overall 5-year survival of 16 per cent. The same authors found that in 56 palliative operations 75 per cent were dead in 6 months. Reviews of the subject by Rodney Smith (1953) and Moore and Younghusband (1954) give a similar impression. Though none of the cases recorded had survived 5 years, the results were definitely better in ampullary carcinoma, and palliative operations were disappointing, with an average duration of life of 5–6 months.

The results obtained by Cattell and Warren (1953) are as yet unequalled and, while the number is small by comparison with other growths, it is interesting to compare their operative mortality of 13·6 per cent and 5-year survival of 16 per cent with the results of operations for cancer in other sites.

Cancer of Œsophagus.—Sweet (1952) in a series of 254 patients with œsophageal carcinoma treated by radical resection had an operative mortality of 11·6 per cent for low growths and 24·3 per cent for those in the mid-thoracic region. Of 211 cases available for post-operative follow-up 16 per cent were alive 3 years later and 5·7 per cent alive 5 years later.

Cancer of the Stomach.—Ransom (1953) reports a series of 1264 patients with cancer of the stomach with an overall operative mortality of 18·1 per cent in those resectable and a 5-year survival of 28 per cent.

Cancer of the Lung.—Price Thomas (1952) reports a 5-year survival rate of 21·15 per cent. Borrie (1952) reports 128 resections with an operative mortality of 22 per cent and considered that 20 per cent of resections were likely to be alive 3 years or more after resection.

The results of pancreatico-duodenectomy for carcinoma of the head of the pancreas are not good, but they can bear comparison with some recognized surgical procedures for cancer in other sites.

From inquiries in this country it is apparent that at least another 4 as yet unpublished cases have survived 5 years after operation and a considerable number have survived 3 years. One case of carcinoma of the common bile-duct died in the sixth post-operative year from hepatic secondaries and another of the ampulla of Vater is alive in the sixth year and free from metastases, but with a locally inoperable carcinoma of the rectum (d'Offay, 1954). A carcinoma of the pancreas died 5½ years after operation from local recurrence (Rob) and an ampullary carcinoma is alive 5 years after resection (Rodney Smith, 1954).

As a supposed contrast to the radical operation, with its high mortality and poor survival rate, palliative short-circuits are favoured by some. Unfortunately in poor risks the operative mortality is not low and attention has already been drawn to the short survival rate obtained in most series with such operations. There are, however, occasionally surprising exceptions with a long survival, though there is seldom histological evidence of the condition found at the time of the palliative operation. A remarkable case is reported by Aird (1954). In 1938 a patient was explored by Vick and found to have an inoperable cancer of the head of the pancreas with twelve secondaries in the liver. A short-circuit was performed and the patient survived. In 1953 the anastomosis silted up and the patient was explored by Aird. There was an irremovable tumour in the head of the pancreas and twelve secondaries in the liver. The common bile-duct was greatly dilated and was anastomosed to the small intestine with such good effect that the patient is still alive sixteen years after the original palliative proceeding. Biopsy of the primary growth at the second operation suggested that it was a malignant ' carcinoid ' tumour.

In general, the surgical opinion expressed has been in favour of radical resection for carcinoma of the ampulla of Vater, but considers operation unjustifiable for carcinoma of the pancreas itself unless the growth is small and easily operable. Difficult dissections around the superior mesenteric vein almost certainly indicate that a radical resection is unwise; there seems little justification for an attempt at resection of the involved portal vein and the division of the neck of the pancreas in cases of doubtful operability may spill cancer cells in the surrounding tissues and disseminate the disease. Operability is not always easy to assess, but ill-chosen cases almost certainly account for many of the early recurrences after radical resection and have given the operation a poor reputation. Radical resection is only indicated for the obviously operable case and, if it is reserved for this group, its after-results may be expected to improve.

SUMMARY

Two 5-year survivals are described following pancreatico-duodenectomy for carcinoma of the head of the pancreas and the results of the operation are discussed.

I wish to acknowledge my grateful thanks to those surgeons who have helped me so readily with details of their cases.

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PANCREATIC LITHIASIS AND CHRONIC PANCREATITIS: TREATMENT BY PANCREATIC LITHOTOMY A TERGO AND RETROGRADE PANCREATICO-JEJUNOSTOMY

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Operations for removal of stones from the pancreas by opening the duct from the lesser sac anteriorly, or, after mobilization of the duodenum and head of the gland, from behind, are difficult always and incompletely successful often. Furthermore, the available methods (Whipple, 1946; Doubilet and Mulholland, 1950; Eliason and Welthe, 1948; Jones and Smith, 1952) for the treatment of chronic pancreatitis (splanchnicectomy, vagotomy, sphincterotomy, and biliary tract drainage) have been disappointing, and total pancreatectomy, though it eradicates pancreatitis, is not a welcome alternative (Waugh, Walters, Gray, and Priestley, 1952). We consequently devised an alternative approach to the calculous duct and in the course of that operation a new alternative treatment of chronic pancreatitis occurred to us.

CASE REPORT

On Jan. 11, 1954, a 42-year-old woman with a history of intermittent bouts of severe upper abdominal pain was admitted to Hammersmith Hospital. As a 7-year-old child the patient experienced abdominal pain similar in nature to that responsible for her admission. She had been told by her mother that such attacks had occurred from infancy. The attacks of pain persisted throughout her early years. The pain came on suddenly without any obvious precipitating cause. It had a knife-like, cutting quality seeming to pass directly through the upper part of her body. There was no relationship noted to food, position, or any environmental factor. After persisting for a few days, the pain would suddenly go. The attacks occurred two or three times a year. There was no associated nausea, vomiting, jaundice, elevation of temperature, rigors, or disturbance in bowel function. While the pain persisted, the patient used to remain in bed and was without appetite. A considerable variety of medications prescribed by the family physician were all ineffectual.

Throughout adolescence these recurrent attacks continued. Between the age of 20 and 25 years, the patient had been admitted to hospital for investigation on four different occasions. Each time a barium meal had been done and the patient had been informed that she was indeed fortunate that no ulcer had been found. An ulcer régime had failed to bring relief. In spite of the persistence of these incapacitating attacks of the pain the patient married and carried on her work as a school teacher.

When she was 34 years of age (March, 1946), it was suggested that her difficulties might be related to chronic appendicitis. An operation was performed but the appendix was found to be quite normal. However, exploration revealed the presence of chronic pancreatitis and multiple calculi within the head and body of the pancreas. Several of these calculi were removed through small incisions into the pancreas. The patient had an uncomplicated post-operative course and remained free from abdominal pain for three years, when she began again to experience attacks of pain of the same character as that noted prior to her operation.

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During the next year the severity of the pain gradually increased, and the attacks occurred more often and were of increasingly longer duration. During her thirty-eighth year a bilateral splanchnicectomy was done in two stages (left, July 8, 1949; right, Jan. 6, 1950).

Fig. 625.—Straight radiograph showing patchy calcification in region of pancreas.

There was some relief after the left splanchnicectomy, but within six months of the second operation there was a severe attack of pain. From this time until her admission to Hammersmith Hospital she continued to have attacks of this same pain coming on three or four times a year and lasting seven or eight days each time. During the attacks the patient developed the habit of wringing her hands, which seemed to help her tolerate the pain somewhat better; on one occasion she dislocated both thumbs during an attack and became aware of the dislocation only after the pain had gone. During the attacks the patient was incapacitated and confined to her bed. Within the last year, the patient began to feel run down, constantly fatigued, and never quite well even during the intervals between the episodes of severe pain. Her appetite remained poor at all times. Perhaps the single most impressive feature of this long history is the extraordinary uniformity of the symptoms in spite of medical and surgical treatment, from infancy onwards. The character of the pain remained the same, varying only in degree, frequency, and duration. There can have been very little psychogenic element in this patient's illness; to have carried out her duties as a wife and teacher in the face of so disabling an illness must have required a very high morale. At the time of her admission the

patient was co-operative and well orientated; she seemed to be about her stated age and to be chronically ill. The skin was pale and dry with loss of elasticity. There was an ill-defined area of tenderness in the epigastrium, with no other signs of abdominal disease. No other

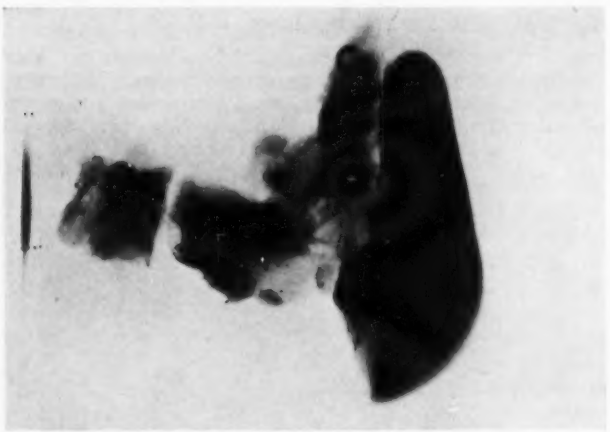

FIG. 626.—Radiograph of specimen of spleen and tail and body of pancreas, showing calculi.

significant physical findings were noted. Plain X-ray examination of the abdomen showed multiple, irregular areas of calcification in the region of the pancreas (*Fig.* 625).

The hæmoglobin was 62 per cent of normal. A glucose-tolerance test suggested mild diabetes although there had been no glucose in the urine. Pancreatic enzyme activity within the stools was normal. The remainder of the investigations, which included a complete blood-count, urine analysis, barium meal, serum-amylase, urine diastase, and prothrombin level, were within normal limits. The patient was given three blood transfusions in preparation for operation.

AT OPERATION.—On Jan. 26, 1954, exploratory laparotomy was carried out through a right paramedian incision. The significant abnormalities were restricted to the area of the pancreas. This organ was grossly enlarged with multiple, very hard, irregular masses palpable within the head, body, and tail. These changes appeared to be maximal in the left half of the pancreas. An incision was made through the peritoneum to the left of the attachment of the lienorenal ligament and through the underlying fascia, and the spleen was mobilized in the usual way together with the tail and body of pancreas and the splenic vessels. A plane for dissection was found without difficulty and there was little evidence of previous retropancreatic inflammation. Mobilization was continued as far as the origin of the splenic artery, which was ligated and divided, and the termination of the splenic vein which was ligated also and divided just short of its junction with the superior mesenteric vessels. The tail and body of pancreas and the spleen were then brought forwards out of the wound and the pancreas was transacted at the left border of the superior mesenteric vein, the distal part of the pancreas being ablated with the spleen. The cut surface of the pancreatic remnant presented a grossly dilated and thick-walled main pancreatic duct which measured more than 1·5 cm. in diameter and which contained loose calculi, some of which attained 1 cm. in diameter. With the use of a gall-bladder scoop it was readily possible to remove large numbers of calculi of various sizes from the pancreatic duct (*Fig.* 628). After removal of the calculi, a probe passed easily through the pancreatic duct into the duodenum, there being no suggestion of obstruction at the sphincter of Oddi. At this stage in the operation various alternatives were considered. We were reasonably certain that all gross calculi had been removed from the remnant of the gland. That remnant was, however, so obviously the seat of a chronic pancreatitis that we were anxious to ensure effective drainage of the duct. Splanchnicectomy had already proved inadequate for this purpose, and previous experience of operations for the diversion of the biliary stream and of the division of the sphincter of Oddi had not impressed us as satisfactory either. It occurred to one of us (J.B.) that the pancreatic remnant might be drained satisfactorily into a Roux loop of jejunum, and that this retrograde route for drainage might avoid the risk of recurrent stenosis and of reflux of duodenal juice which theoretically the operation of sphincterotomy carries. Accordingly the jejunum was divided about 18 in. distal to the ligament of Treitz. The stump of the remaining pancreas was implanted into the distal end of the transected jejunum by two rows of silk sutures. The continuity of the jejunum was re-established by end-to-side anastomosis of the proximal jejunal end to the jejunal Roux loop 12 in. distal to the pancreatic-jejunal anastomosis (*Fig.* 629). The patient tolerated the operation well.

PATHOLOGY. — Microscopical examination of the excised pancreas showed marked fibrosis with preservation of a surprisingly large amount of islet tissue (*Fig.* 627). The pancreatic ducts were dilated and had markedly thickened walls of little more than fibrous tissue. Signs of inflammation were conspicuous by their absence. Chemical analysis of the calculi showed them to be composed mainly of calcium carbonate. A radiograph of the excised tissue is shown (*Fig.* 626).

PROGRESS.—The immediate post-operative course was complicated by the development of a diabetic state requiring insulin therapy. A glucose-tolerance test later showed a diabetic type of curve. The patient was discharged from hospital one month following operation.

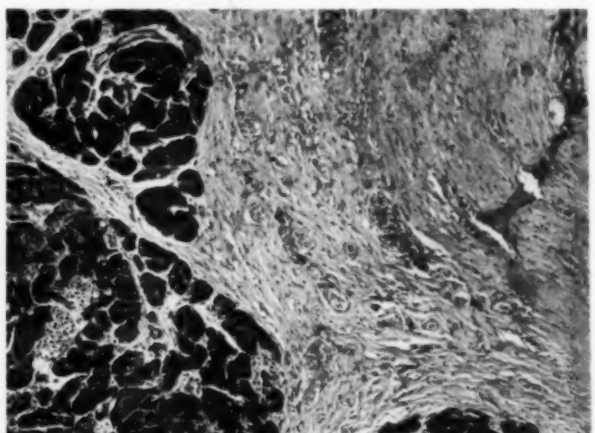

FIG. 627.—Photomicrograph of section from removed pancreas showing dilated ducts and periductal fibrosis with surprisingly large amount of islet tissue. (× 60.)

At this time she continued to have a mild diarrhœa and required 10 units of soluble and 10 units of protamine zinc insulin daily to control her diabetes. She remained pain-free, had an excellent appetite and stated that she now felt better than at any time during the five years prior to the operation. This improvement was reflected in a marked change of mood. Her mild depression before operation and the resignation incident to the prolonged discouraging course of her illness, was replaced by a constrained optimistic and hopeful attitude. Four months following operation her insulin requirements remain the same. There has continued to be some troublesome diarrhœa which is now definitely decreasing in degree. Her appetite remains good, she has gained

weight, has resumed her duties as a housewife and schoolteacher, and has been entirely free of pain.

There is no question that this patient still suffers from a degree of pancreatic insufficiency. This is reflected histologically in the state of the gland on microscopic section. Perhaps the best clinical yardstick of this insufficiency is the patient's diarrhœa, which is unquestionably improving spontaneously as time goes on; there are now three or four stools daily. Vitamin-A absorption studies show that this patient suffers from a defect of iron absorption from the alimentary tract, and she still has a pronounced tendency to anæmia. After a course of intravenous iron her hæmoglobin has now, however, reached 85 per cent; it seems likely that further intravenous iron will be necessary for her. The behaviour of her blood-picture has been quite complicated, and it would seem undesirable to try to report it fully in this paper; indeed, a substantial period of follow-up will be required before full data are obtained about it for analysis.

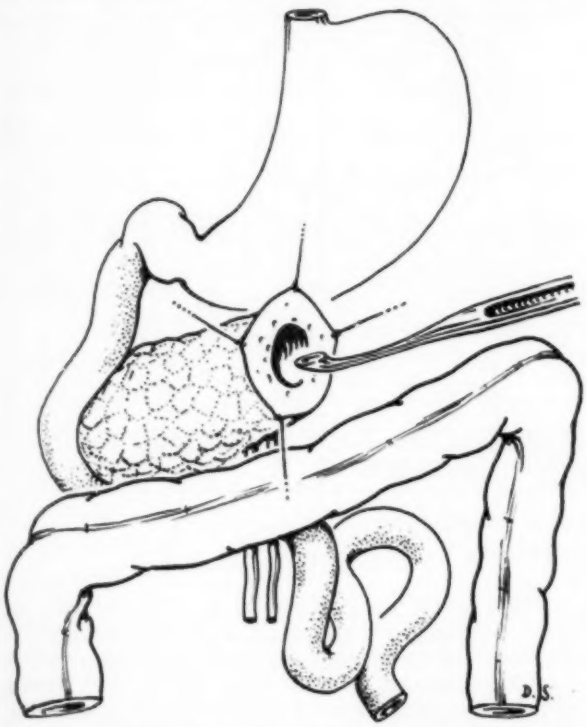

FIG. 628.—Method of removal of stones from remnant of pancreas after removal of tail and body with spleen.

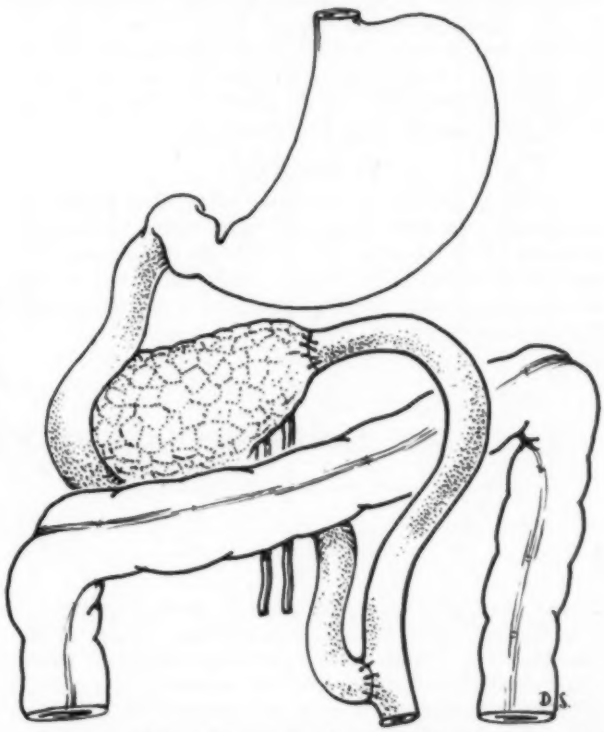

FIG. 629.—Method of anastomosis of divided end of pancreas to Roux loop of jejunum.

COMMENT

This patient has thus suffered from pancreatic lithiasis and from its effects, reflected pathologically in an obstructive pancreatitis, over a period of very many years. The operation of pancreatic lithotomy *a tergo* which was adopted in this case proved satisfactory for the removal of calculi. The access which transection afforded to the right extremity of the duct in the head as far as the ampulla of Vater was entirely adequate.

It is impossible to say whether the pancreatic calculi in this case, as in others, had resulted from a primary anatomical or functional failure of the duct to open adequately into the duodenum, or whether an obstructing calculus (or calculi) was responsible for dilatation of the duct system which obtained at the time of operation.

This patient's recurrent symptoms of disabling pain have all been suggestive of a recurring acute pancreatitis, though the pathological findings in the part of the gland removed suggest that this pancreatitis was obstructive rather than inflammatory. The operation of retrograde pancreatico-jejunostomy offers a new route for the drainage of a pancreas the seat of chronic or relapsing pancreatitis of this obstructive type. If, as seems not unlikely, all relapsing pancreatitis is associated with a high tension in the pancreatic duct system, pancreatico-jejunostomy of this retrograde type might be applicable to relapsing pancreatitis in general. When in fact, a fistula that results from the drainage of an abscess after pancreatitis is implanted into the jejunum, this very operation is performed in two stages; and when a pancreatic pseudocyst, the result of pancreatitis, is anastomosed to the jejunum, a similar kind of effect is indirectly achieved. R. B. Cattell (Cattell and Warren, 1953, 1954) has suggested implantation end-to-side of a jejunal Roux loop into the dilated pancreatic duct in such circumstances, and has performed this operation to relieve the pancreatic obstruction proximal to an inoperable malignant block. We understand also that John M. Waugh has supplemented the effect of sphincterotomy by excising the tail of the pancreas and implanting the left end of the duct into jejunum. These operations, like retrograde pancreaticojejunostomy, are methods of decompression of the pancreatic duct system. In this respect a case recently reported by Goethe (1953) is particularly illuminating; this patient suffered from pancreatic calcification which was treated by external pancreatostomy (Goethe, 1911); during forty-two years after

this operation the patient remained essentially free from pain, while continuing to pass calculi from the fistula. Internal pancreatostomy would seem to have no fewer advantages than external pancreatostomy, and avoids all the inconvenience of an external pancreatic fistula. In the operation we performed the use of the transected pancreatic duct, after removal of spleen and tail and body of pancreas, appeared to us more manageable for lithotomy and jejunal drainage than would have done a lateral opening in the duct. A similar retrograde pancreaticojejunostomy would seem to offer advantages as a supplement to cholecystenterostomy in the treatment of inoperable ampullary malignant disease.

SUMMARY

1. An operation is described which has facilitated removal of stones from the pancreas. It entails removal of the spleen, tail, and body of the pancreas and extraction of the stones from the head of the gland through the dilated duct, which is thus opened on the transected surface.

2. A method of drainage of the pancreas applicable to chronic pancreatitis, perhaps also to inoperable malignant disease, is also described. After ablation of the left part of the gland with the spleen, the cut surface of the remnant is implanted end-to-end in a Roux jejunal loop.

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THE TREATMENT OF DUODENAL ULCER BY VAGOTOMY AND GASTRO-JEJUNOSTOMY

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THERE is no unanimity of opinion amongst surgeons as to the operation which gives the best results in the treatment of chronic or relapsing duodenal ulcer. Most surgeons favour partial gastrectomy, which gives good results in a large proportion of cases, but it does not eliminate the risk of recurrent ulceration, and in an attempt to lessen this risk some resect all the stomach except the fundus. Although this latter procedure almost entirely removes the risk of stomal ulceration, it leaves a number of patients unable to maintain their weight and energy and unable to carry on their work. Subtotal gastrectomy can be criticized as being too drastic a method of curing duodenal ulcer, particularly in young patients, and so the search for other measures has continued.

The re-introduction of vagotomy by Dragstedt offered a new approach to the problem. The early failures are now merely historical and the limitations of simple vagotomy well known and avoidable. The gastric atony and retention are overcome by the addition of such procedures as pyloroplasty, gastrojejunostomy, and limited gastric resection which allow the stomach to empty easily. During the past few years reports of the results of these combined operations have been published, but in most cases the number of patients treated is small or the follow-up period short. More evidence is required before surgeons can be expected to decide on the relative merits of the different forms of treatment. As recently as 1952 the American Society of Gastroenterologists, after an extensive inquiry, reported that subtotal gastrectomy is still the operation of choice for duodenal ulcer, but on reading the evidence they produced it is not clear how they came to reach their conclusion.

This article is written with the object of providing more evidence on the results of the treatment of duodenal ulcer by vagotomy and gastrojejunostomy. The combination was selected for several reasons, not the least important of which was the desire to use the simplest and safest operation on the stomach, so that, if it came to be generally adopted, it could be used by surgeons of relatively limited experience without any increase in mortality. From this point of view gastrojejunostomy appeared to be preferable to pyloroplasty and gastric resection. It had the added attraction that by itself it gives good results in the treatment of duodenal ulcer. Its only serious drawback is that it may be followed by stomal or jejunal ulceration, a complication brought about by the persistent secretion of highly acid gastric juice in the duodenal ulcer patient. This secretion is known to be largely neurogenic in origin and is abolished by vagotomy, so that on theoretical grounds the combination of these two measures appears to be sound.

MATERIAL

The results reported are those from a consecutive series of 243 patients operated on between October, 1947, and July, 1953. During this period all patients with duodenal ulcer referred to one of us (R. L. H.) for surgical treatment were treated by vagotomy and gastrojejunostomy except for those who were operated on as emergency cases of perforation or hæmorrhage. Recent hæmorrhage which had responded to medical measures was not regarded as a contra-indication and numerous such cases are included in this series. Most of the cases were referred for treatment by medical colleagues, and

surgical treatment has not been offered to any of the patients who have not previously had a suitable course of medical treatment. No private patients have been included and the series consists of patients drawn from a population largely industrial in occupation and living under conditions which are not always ideal for the ulcer patient. An appreciable proportion of the patients have been operated on by surgeons of Senior Registrar grade so that results obtained cannot be related entirely to the experience of the operators. In fact it is felt that under the conditions employed the treatment has been given a fair and searching trial.

Some of the relevant statistical details of the 243 patients are given in *Table I*. There can be no doubt about the chronicity of the duodenal ulcers —81 per cent of the patients had had symptoms for over five years. A considerable proportion of them had previously had either hæmorrhage, a perforation, or both, and many had clinical and radiological evidence of stenosis.

The percentage of women in the series is 12 per cent, a lower proportion than the figures of relative incidence quoted by Illingworth (1953), and over 70 per cent of the women had had symptoms more than 5 years.

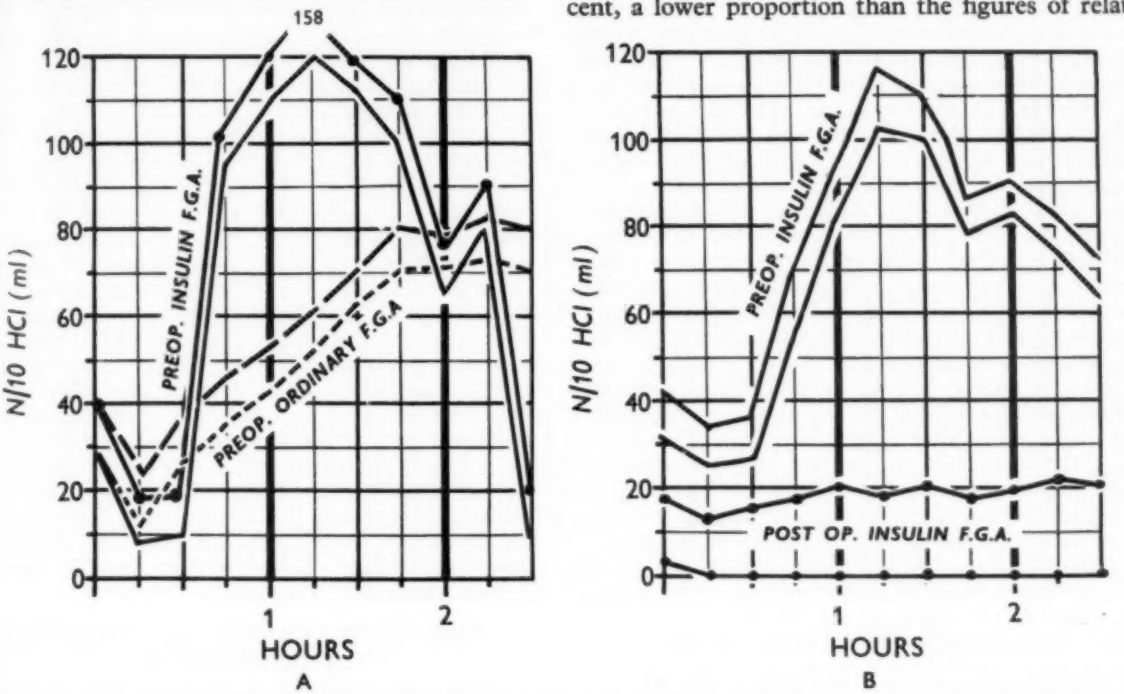

FIG. 630.—A, Comparison of consecutive F.G.A. results in the same patient. Upper curve—an insulin F.G.A. Lower curve—an ordinary (gruel) F.G.A. B, Comparison of insulin F.G.A. results pre- and post-operatively. Upper curve—typical reponse shown by a duodenal ulcer case. Lower curve—from the same patient after complete vagotomy, which has produced achlorhydria.

Table I.—DETAILS OF 243 CASES

Age at Time of Operation

	15–20 yr.	21–40 yr.	41–60 yr.	Over 60 yr.
Males	4	87	115	8
Females	1	7	19	2
Total	5	94	134	10
	(2 per cent)	(38 per cent)	(55 per cent)	(4 per cent)

Length of Ulcer History

	1–5 yr.	5–10 yr.	Over 10 yr.
Males	37	53	124
Females	8	5	16
Total	45	58	140
	(18·5 per cent)	(23·9 per cent)	(57·6 per cent)

Pre-operative Complications

	Perforation	*Hæmorrhage*	*Stenosis*
Males	29	49	20
Females	3	5	3
Total	32	54	23
	(14 per cent)	(22 per cent)	(9 per cent)

Pre-operatively nearly all the patients had an insulin fractional gastric analysis and very high levels of gastric acidity were found almost invariably. Age, length of history, and stenosis did not appear to be sufficient to damp down the potential secretory activity of the stomach. The so-called burnt-out duodenal ulcer was singularly absent in this series, although it includes a number of patients over 60 years of age and many with a 20 or more years' history of dyspepsia. There was not a single case in this series in which hypochlorhydria was found. In some of the early cases the ordinary gruel F.G.A. was used as well, but it was soon given up since it was very obvious that the results obtained bore no relationship to the true secretory levels of the patients' gastric mucosa (*Fig.* 630 A).

OPERATIVE TECHNIQUE AND POST-OPERATIVE MANAGEMENT

It is not intended to give a lengthy account of our actual technique. The subdiaphragmatic vagotomy is carried out in a manner similar to that described by Dragstedt (1945) except that a left paramedian incision is used and the left lobe of the liver is not mobilized. From 3–4 cm. of each vagus nerve is excised and the cut ends ligated with linen thread. Particular care is taken to break any filaments of the

anterior vagus nerve entering the lower 5–8 cm. of the œsophagus. The gastrojejunostomy is posterior, horizontal, and isoperistaltic. The stoma is about 6 cm. in length and placed as near the pylorus as is conveniently possible. Post-operatively the stomach is kept empty by suction through a Ryle's tube and the suction is maintained until it is quite evident that the upper gastro-intestinal tract has recovered from its temporary paresis. Drinks in measured and restricted quantities are allowed as soon as the patient recovers consciousness, but the fluid balance is maintained by a continuous rectal drip. Blood transfusions are not given except as part of the treatment of patients who have bled before operation. As a rule the Ryle's tube can be removed on the third day, but cases have occurred in which it has had to be retained for as long as ten days. Once the Ryle's tube is removed the patient progresses rapidly towards a light diet and then on to a normal diet. Before he leaves hospital he is deliberately given a relatively indigestible meal as it is felt important to demonstrate practically to himself and his family that dietary restrictions are no longer necessary. These measures and the rest of the post-operative management are designed to help in removing the atmosphere of invalidism that surrounds so many duodenal ulcer cases. Early ambulation plays a large part in this. Patients are allowed up on the first post-operative day and generally walk unaided to the end of the ward on the third day. The low incidence of post-operative complications is probably in large part due to this early resumption of activity after operation.

MORTALITY

As might be expected from the simplicity of the operation, the mortality is low—there has been only 1 death in the 243 cases. This patient died three days after operation as a result of continuous diarrhœa, cholera-like in its severity, which would not respond to treatment. A post-mortem examination, though disclosing evidence of bronchopneumonia, failed to reveal any cause for the diarrhœa.

POST-OPERATIVE COMPLICATIONS

Serious complications have been almost entirely absent. The commonest trouble has been the post-operative ' chest ', which has occurred in 25 per cent of the patients. It has usually been very transient and has consisted of a rise of temperature lasting two to three days, with a productive cough. A number of patients showed unmistakable signs of atelectasis, but this has responded on each occasion to physiotherapy. All the complications are listed in *Table II* and require little further comment. The dysphagia in 3 out of 4 cases cleared up within a few days without treatment. In the remaining case it persisted, but a radiograph showed no abnormality in the œsophagus and a complete cure followed immediately after œsophagoscopy.

Table II.—Post-operative Complications

Chests ' (Bronchitis, collapse, and bronchopneumonia)	61 (25 per cent)	Wound infection	2
		Femoral thrombosis	1
Dysphagia	4	Lobar pneumonia	1
Prolonged ileus	2	Hepatic cirrhosis	1

Diarrhœa, except in the single fatal case, has not been troublesome. Whilst a number of our patients have had a transient period with diarrhœa in the immediate post-operative period others have had a tendency to constipation and this apparently contradictory state of affairs has been noticed in the later follow-up. Mention has already been made of the patients who had signs of gastric retention up to ten days after operation. These were 2 in number and there were no signs or symptoms to suggest that the gastric or intestinal paresis was due to a localized peritonitis. In each case the condition cleared up without any special measures other than the maintenance of fluid balance and continuous gastric suction. The relationship between the operation and the development of hepatic cirrhosis in one patient has never been quite clear. The man left hospital apparently perfectly well but was re-admitted a fortnight later with some ascites and slight jaundice. Now, more than two years later, he appears to be perfectly well except that he has to take some care with his diet. The absence of any serious post-operative morbidity is shown by the fact that 44 per cent of the patients went home on the twelfth day after operation, a further 44 per cent within fourteen days, and in the remainder the cause of further stay in hospital was usually due to delay in arranging laboratory investigations, particularly post-operative insulin fractional gastric analysis.

THE PERCENTAGE OF COMPLETE VAGOTOMIES

Vagotomy does not necessarily make the patient achlorhydric, as it can only abolish the fraction of the secretion which is neurogenic in origin. The secretory response to the presence of food in the stomach remains unaltered, and this is perhaps its main advantage over the other surgical methods of reducing gastric acidity in that it leaves the patient with some gastric digestion. What vagotomy does is to abolish the characteristic continuous secretion of highly acid and proteolytic gastric juice of neurogenic origin which has been proved to form the most important fraction of the secretion in duodenal ulcer.

The insulin fractional gastric analysis is used as a test of the completeness of a vagotomy. Normally in the duodenal ulcer patient a lowering of the blood-sugar to 50 mg. per 100 c.c. is followed by a very steep rise in the acidity of the gastric juice. The typical response shows acid levels which rise above those catered for in the usual hospital chart (*Fig.* 630 A). It includes a fall in acidity which takes place when the resting contents are removed and the steeple-like response to the hypoglycæmia, involving a rise to levels which often exceed 100 units (expressed in terms of c.c. of N/10 HCl in 100 c.c. of the specimen). A complete vagotomy abolishes this rising response, as shown in the lower curve in *Fig.* 630 B which is taken from a case where achlorhydria has also been produced. As an arbitrary standard it has been suggested that a rise in the gastric acidity of more than 30 units within two hours after the lowering of the blood-sugar to below 50 mg. per 100 c.c. should be regarded as evidence of incompleteness of the vagotomy. This standard has been used in compiling our results in *Table III*. There is no doubt about

the acid response in an incomplete vagotomy. A typical example is shown in *Fig.* 631, in which the response to the hypoglycæmia is so marked that it cannot be masked by the presence of large amounts

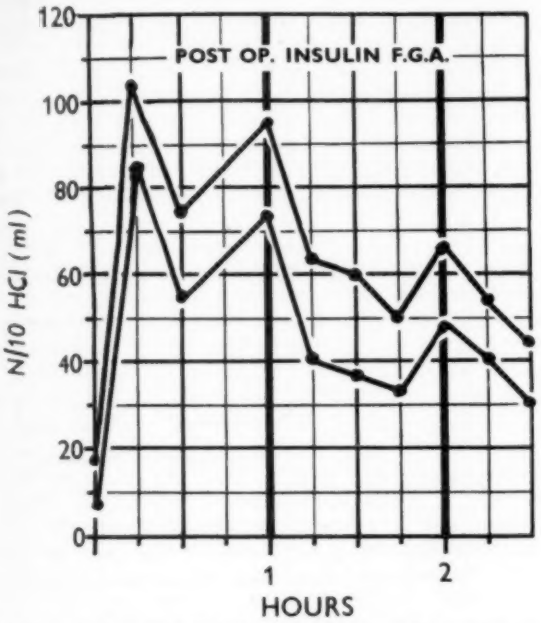

FIG. 631.—Insulin F.G.A. in a case of incomplete vagotomy, with no doubt as to the incompleteness.

of bile in the gastric contents. But in many of these patients the rise in acid level is between 30–35 units, as shown in *Fig.* 632, and whilst included in the incomplete vagotomy category they are more likely to be in fact cases of complete vagotomy. *Fig.* 633 shows a late type of response seen occasionally in the incomplete vagotomy cases.

As already indicated, complete vagotomy is not necessarily followed by a complete absence of free acid in the gastric juice. In a proportion of the cases hypochlorhydria occurs. Patients with hypochlorhydria have been subdivided into two groups according to the amount of acid in the resting contents, viz., 0–20 units and 20–40 units. In each of these groups (*Figs.* 634, 635) there may be a slight rise in the acid values during the test, but in neither group does the extent of the rise exceed 30 units.

Table III.—COMPLETE AND INCOMPLETE VAGOTOMIES

Complete Vagotomy (88 per cent)	215	Achlorhydria	113
		Hypochlorhydria Resting juice 0–20 units	72
		Hypochlorhydria Resting juice 20–40 units	30
Incomplete vagotomy	27		

Table III shows that nearly half of all the patients come into the achlorhydric group, very nearly as many into the hypochlorhydric group, and 12 per cent with an acid rise of 30 units or more, into the incomplete vagotomy group. When it is remembered that quite a number of the 'incomplete' results are probably actually 'complete', as indicated in the last paragraph, the percentage of incomplete vagotomies appears more reasonable.

RESULTS

The symptoms of duodenal ulcer, if those of its complications are excluded, are mainly subjective and, as a result, the assessment of the success or

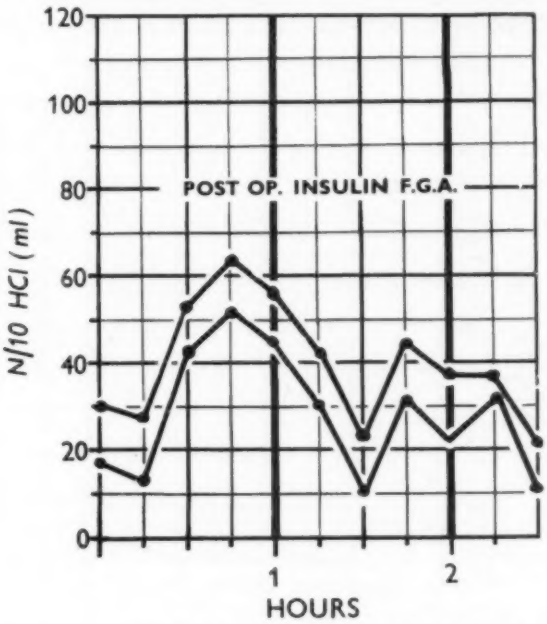

FIG. 632.—Insulin F.G.A. in a case of doubtfully incomplete vagotomy, with an acid rise of only 34 units.

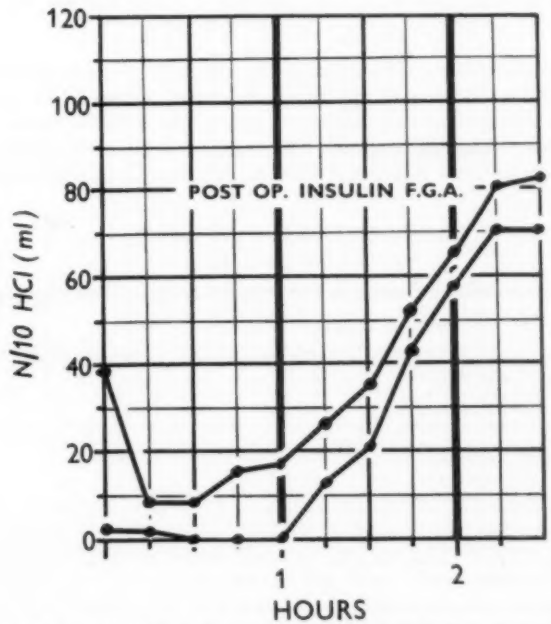

FIG. 633.—Insulin F.G.A. A less common type of result met with in incomplete vagotomy.

failure of a particular method of treatment is not easy. The operation may cure the patient of his ulcer pain and leave him with a secondary set of symptoms which can be as troublesome as his original ulcer. The patient may blame all his symptoms on his operation, even those present before it and those completely unrelated to his ulcer, or he may be very pleased with the result but on close questioning

appear to have such troublesome sequelæ that the surgeon is forced to put him into the group of unsatisfactory results. The follow-up examination is better done by the same individual on each occasion and by personal interview rather than written questionnaire, although it is fully realized

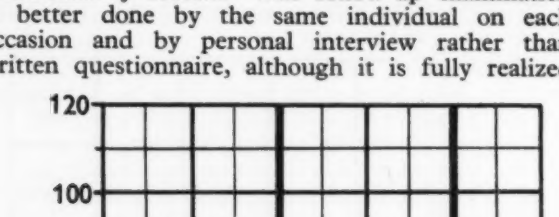

FIG. 634.—Insulin F.G.A. Complete vagotomy with less than 20 units of free acid in the resting contents.

that this is apt to result in the recording of complaints which ordinarily would have been allowed to pass as insignificant. This has been the arrangement in this series of cases. One of the major difficulties experienced has been that of keeping in contact with

Table IV.—OVERALL 3-YEAR RESULTS
(110 patients)

VISICK'S GRADING	MALES	FEMALES	TOTAL	
1. No symptoms	67	10	77	87 per cent Satisfactory
2. Mild symptoms, easily controlled	14	2	16	
3. Mild symptoms, not controlled, but S (satisfactory)	3	0	3	
3. As 3 S, but U (unsatisfactory)	9	4	13	13 per cent Unsatisfactory
4. Not improved	1	0	1	

all the patients. In spite of all reasonable precautions 5 per cent of our patients become untraceable after three years. A second difficulty is that of presenting the results in a manner which is simple and allows easy comparison with those published in other papers. It is customary to divide the results into satisfactory and unsatisfactory, but each surgeon seems to adopt a different method of assessment. In general the success of any operation for duodenal ulcer is decided on whether or not (1) it cures the original ulcer and its symptoms, and (2) it is followed by evidence of recurrent ulceration. These are obviously essential criteria of success, but consideration should be given to the minor annoyances which may follow any gastric operation. In this respect Visick's grading (1948) appears to offer the best means of classification.

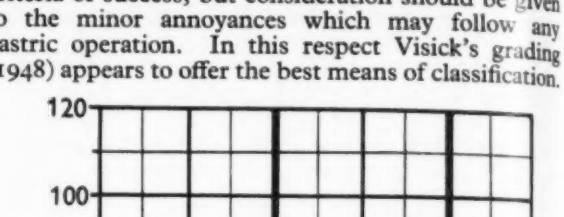

FIG. 635.—Insulin F.G.A. Complete vagotomy with between 20 and 40 units of free acid in the resting contents.

But merely to rely on an overall tabulation of the results would give a false impression, and to avoid this all the serious complications which have occurred have been recorded along with an account of the minor sequelæ.

The immediate results of vagotomy and gastro-jejunostomy, like those of any other operation for duodenal ulcer, are excellent. There is an immediate relief of ulcer pain, the patient is able to enjoy a full and varied diet, and he is able to return to his old work. All experienced surgeons are aware of the pitfalls of this initial success. Accordingly only those patients who were operated on more than three years ago have been included in our results. Three years may prove to be too short a follow-up period on which to judge this operation. Some complications, such as gastric ulcer, may take longer to appear, but others, such as stomal ulcer, will in most cases have shown up within three years. There are 124 patients in this group, of whom 6 remain untraced; 8 others have died since operation of the causes which were unrelated either to the operation itself or the original duodenal ulcer (pemphigus and bronchopneumonia 1, coronary thrombosis 1, carcinoma of rectum 1, glioblastoma multiforme 1, *salmonella* gastro-enteritis 1, nephritis Ellis type 2 1, miliary tuberculosis 1, acute gastro-enteritis 1). The overall results in the 110 cases left for detailed consideration are given in *Table IV*.

In this assessment Visick's grading has been interpreted as follows:—

Grade I: Patients who are symptom-free, enjoying a full diet, not requiring medicines, working

full-time, and completely satisfied with the result of the operation.

Grade II : Patients who have mild gastro-intestinal complaints which are easily controlled, who are working full-time, and are satisfied with the result of the operation.

Grade III, S : Patients who have mild residual symptoms which are not fully controlled by simple precautions. These patients are working and do not find their symptoms a hindrance.

Grade III, U : Patients with residual symptoms who are not satisfied with the result of their operation or patients considered by us to have an unsatisfactory result.

Grade IV : Not improved.

These figures are deliberately weighted towards the 'unsatisfactory' side. A strict standard has been employed and every patient expressing dissatisfaction with the operation had been included in the unsatisfactory group. This group also includes patients who, whilst working full time and expressing satisfaction with the result of the operation, are regarded in our opinion as having sufficient abdominal discomfort to be properly recorded as unsatisfactory.

Unsatisfactory Results.—Nothing is to be gained from a study of the satisfactory cases except to remark that the patient who is determined to do well almost always seems to end up with a good result, and the introspective, uncertain type, with a poor one. The less satisfactory cases are worth while studying in some detail. They have been subdivided into two groups : (1) those having signs or symptoms of persisting, recurrent, or stomal ulceration ; and (2) those classified as unsatisfactory (Grade III, U) in *Table IV*.

1. *Persisting, Recurrent, or Stomal Ulceration.*—There has been no evidence of the persistence or recurrence of the original duodenal ulcer in any of the patients in this series. Only 2 patients have complained of pain which in any way resembles that of their original ulcer. Both have been thoroughly investigated without the discovery of any confirmatory evidence of active ulceration in the stomach, duodenum, or jejunum. One of the two is being kept under observation as a possible, but as yet non-proven, case of stomal ulcer. Two other patients have had hæmatemesis. One of them was admitted to a London Hospital and has had a partial gastrectomy for stomal ulcer. The other was re-admitted to our own hospital and fully investigated, but no organic cause for the hæmatemesis could be found. He was a heavy drinker and it was thought that the hæmatemesis might be related to his habits. In the series as a whole perforation has not occurred in any patient post-operatively and radiological examination of those with post-operative symptoms has not shown any evidence of continued or renewed ulceration.

2. *The Group III, U in Table IV*.—The patients who have found their way into this group have done so not as a result of any serious complication but by reason of a combination of minor annoyances. It has been thought worth while to give an account of the unsatisfactory features in each case. These are set out in *Table V*.

The higher incidence of unsatisfactory results in the female cases is at once apparent, but it is to be noted that 2 out of the 4 are menopausal and 1 has a chronic anxiety state. All of them have some gastric or other disturbance which might fairly be related to their operation, but the impression remains that these complaints might have been discounted by the patients if there had not been the additional factor mentioned above. The commonest complaint in the group has been that of bilious vomiting. It has been present in all the females and 5 out of the 9 males. In 2 of the men it has been the sole cause of the unsatisfactory results. In about half of the cases it has occurred throughout the follow-up period and in the other half it has developed after a period of two to three years. It is an odd complaint, lessening in severity, or disappearing completely when the patient is admitted to hospital. Half the patients with it look well and have not lost weight, X-ray examination of the gastro-intestinal tract has shown no abnormality in any of them and it is worth noting that the vagotomy has been complete in every case. There is no doubt that the vomiting does actually take place, but in some cases it only occurs

Table V.—Analysis of Unsatisfactory Results

Males	Age	Symptoms	Ability to Work	Time of Relapse
1	48	Dumping and diarrhœa	Full time	From beginning
2	32	Bilious vomiting and dumping. Diet restriction. Pre-op. symptoms not related to ulcer	Not working	From beginning
3	53	Poor energy and dumping	Working with recent lost time	5 yr.
4	45	Very well except for bilious vomiting	Working with lost time	4 yr.
5	47	Slight dumping. Diet restricted	Full time at lighter job	4 yr.
6	28	Poor energy. Loss of weight. Diet restriction. Bilious vomiting and dumping	Not working	2½ yr.
7	58	Bilious vomiting. Diet restricted	Lighter job	From beginning
8	50	Bilious vomiting getting worse	Working but some lost time	3 yr.
9	18	Loss of energy and appetite	Working with loss of time	2 yr.
Females				
1	40	Bilious vomiting. Dumping, poor energy	Housewife	From beginning
2	51	Bilious vomiting. Anxiety state	Not working*	3½ yr.
3	45	Bilious vomiting, dumping, diarrhœa	Working with some lost time	From beginning
4	44	Bilious vomiting, poor energy	Housewife	Getting worse from beginning

* On account of hypertension and fibrositis.

occasionally and the complaint is really one of regurgitation of a small quantity of bitter fluid into the back of the throat. One of the two patients in whom it has been particularly troublesome has been submitted to operation. The findings were completely negative, the stomach and stoma were normal, the duodenal ulcer was healed, and the pylorus not stenosed.

The next complaint in order of frequency has been the collection of symptoms which quite erroneously are ascribed to 'dumping', viz., a feeling of fullness after meals accompanied by sweating and feeling faint. These symptoms have not been severe except in one patient and he is gradually improving.

Loss of energy, diarrhœa, and some restriction in diet complete the list of complaints. None of them have been in themselves particularly troublesome, but it is noticeable that the majority of these unsatisfactory patients have several complaints. It is this multiplicity of symptoms together with the fact that some of them are, whilst working, having to take time off work which has put them into the unsatisfactory group. Another point to note is that in half the cases the troublesome symptoms have developed two or more years after operation. These late relapses have to be balanced against other symptoms, e.g., dumping and diarrhœa, which appear to lessen in severity with the lapse of time.

Finally, it cannot be without significance that 7 of the 14 patients in the group possess a very obvious psychological background to the symptoms which they present for the surgeon's attention.

Minor Sequelæ of Operation.—A certain number of patients in the satisfactory result groups suffer in a mild form from one or other of the various symptoms experienced by those in the unsatisfactory groups. These symptoms are easily controlled by minor restriction of diet or avoidance of heavy work, except in the case of three patients who continue to have a little trouble which, however, is not sufficient to interfere with their work or their enjoyment of life.

The milder form of 'dumping' differs little from the feeling of fullness often experienced by healthy people after a hearty meal. It does not amount to a real discomfort, and is not accompanied by sweating and palpitation which only occur in the severer forms. The more severe forms of bilious vomiting may also be accompanied by sweating and palpitation and by some discomfort in the upper abdomen, usually on the left side, with radiation to the region of the scapula. In the satisfactory patients bilious vomiting can occur for no apparent reason as an isolated incident, but it is not common and the occasional regurgitation of bile, wrongly described as 'acid', into the pharynx is the more usual picture and has a tendency to occur in the mornings before breakfast. The bilious vomiting in the few severe cases is almost cumulative in character. Their discomfort increases steadily and is dramatically relieved by vomiting a large volume of bile or a mixture of bile and food. Two patients can induce regurgitation of bile by stooping downwards, and in these some secondary effect of the vagotomy operation on the cardiac sphincter seems likely. Dysphagia has not been a troublesome complaint. Two patients mention it, but it only occurs when they attempt to swallow large pieces of meat, bread, or potatoes.

Many patients describe an increased frequency of bowel action to 1–2 per day as compared with 1 or less pre-operatively. An attack of diarrhœa may follow a cold. Some patients find that a tendency to diarrhœa is lessened if they restrict the amount of fat in their diet, others find it necessary to restrict the 'roughage' in their diet. Diarrhœa is often mentioned as a troublesome complication of vagotomy, but it has not proved so in this series.

Table VI.—Minor Post-operative Sequelæ (110 cases)

Entirely free of symptoms					77 (70 per cent)
Bilious vomiting	Severe	3	Anæmia		2
	Moderate	7	Vitamin-B deficiency		2
	Slight	9			
Dumping	Severe	1	Diarrhœa	Severe	0
	Moderate	6		Moderate	3
	Slight	9		Slight	4
Eat anything					83 (75 per cent)
Dietary restrictions	Fat restriction	23	All symptoms are graded by the degree of resulting distress		
	Quantity restriction	4			
	Other food restrictions	7			

Abdominal pain has been conspicuous by its absence in the whole series, except for the two cases mentioned previously who complain of pain after food. Anæmia has occurred in only 2 cases, one of which also showed signs of vitamin-B deficiency. There has been only one other case of vitamin-B deficiency in the series.

Some idea of the incidence of these various symptoms can be gained from *Table VI*, which applies to all the cases in the series, both satisfactory and unsatisfactory.

Other Factors for Consideration.—It has already been pointed out that the success or failure of any particular operation cannot be judged solely on such factors as freedom from ulcer pain and freedom from recurrent ulceration. The object of treatment should be to restore the patient to as near normal as possible and this involves leaving the patient able to work, to enjoy a free and full diet, to maintain his weight and energy, and be free from minor troublesome discomfort.

Ability to Work.—On the whole the duodenal ulcer patient is active, healthy, and not prone to taking time off from his work without good cause, and one of the reasons which influences the older patient in particular to favour surgical treatment is an economic one. Any operation for duodenal ulcer must, if it is to be regarded as successful, result in a very high proportion of patients who are able to carry on their old work. *Table VII* summarizes this aspect of our results and it is satisfactory to note that only 2 out of 97 of those available for work are not working.

Maintenance of Energy and Body-weight.—To a large extent the patient's ability to work is dependent

on his physical well-being. This is difficult to assess and more difficult to control. Some of our patients were overweight before operation and many of them underweight. Many of them were more than 50 years old at the time of operation and might reasonably be expected to have less energy as they got older. On the other hand to most patients one of the more irksome aspects of medical treatment is the restriction it imposes on diet, smoking, and drinking. There is no doubt that many of our patients enjoy their new freedom after operation somewhat unwisely, but it is worth recording that 75 per cent of them eat anything they feel like and a further 16 per cent have only one restriction and that is the amount of fat in their diet. In *Table VIII* the changes in weight and energy are given.

Table VII.—Work Analysis

	No. of Cases		*No. of Cases*
Available for work	97	Lighter job full time	9
Not working	2	* Other job full time	8
Working	95	Not available for work	13
Working, but not full time	7	Housewives	6
Working full time	88	Previous invalidism	1
Old job full time	66	Retired at age limit	3
Heavier job full time	5	*Otherwise retired	3

* Patients in the 'other job' and 'otherwise retired' categories, have changed jobs or retired for reasons unconnected with the operation.

Table VIII.—Details of Maintenance of Energy and Weight

	Energy	*Weight*	*No Information*
Increased	3	62	
Unchanged	75	31	1 case
Decreased	31	16	

A final comment on these results is that the majority of the patients who state that they have less energy after operation are amongst those who gained weight.

DISCUSSION

It is worth while outlining the criteria on which the success of any particular operation for duodenal ulcer can be judged. To be successful the treatment must :—

a. Have a very low mortality,

b. Cure the original ulcer,

c. Not be followed by evidence of further ulceration, e.g., ulcer pain, hæmorrhage, or perforation,

d. Enable the patient to do his full work,

e. Enable the patient to enjoy a full diet,

f. Not to be followed by gastro-intestinal disturbances which seriously interfere with the patient's comfort or work.

In brief a successful treatment should enable the patient to live a normal life and it should be equally effective in young as well as older patients. Obviously no operation for duodenal ulcer is likely to be completely successful since of necessity all alter the physiology of the upper gastro-intestinal tract. For other reasons there are a proportion of patients who are unlikely to be completely cured of their symptoms by any form of treatment. Tanner's remarks (1951) on post-cibal symptoms following gastric operations can be applied much more widely. He stated in his lectures on Peptic Ulceration to the Edinburgh Medical Society : "The most important factor in prevention is to pick cases for surgery who are really most anxious to get well . . . A patient who has suffered agony from his ulcer for years will minimize even severe post-cibal symptoms." This has certainly been our experience not only in regard to post-cibal symptoms but also all post-operative abdominal disturbances. If some policy of selection on these lines had been adopted there is no doubt that our results would have been better, but without any such selection they appear to be most encouraging. The mortality has been less than 0·5 per cent, the incidence of stomal ulcer less than 1 per cent; 90 per cent of the patients available for work are at full-time work without losing time, a further 7 per cent are working in full-time employment with occasional time lost, and 75 per cent are enjoying a normal and unrestricted diet. The unsatisfactory results, with the exception of the one stomal ulcer, have been due to a combination of minor sequelæ, aggravated in some cases by such factors as the menopause, anxiety states, and other symptoms unrelated to the duodenal ulcer.

There are not many published results of the treatment of duodenal ulcer by vagotomy and gastrojejunostomy in the surgical literature. Tanner has grouped his results of vagotomy and gastrojejunostomy with those of vagotomy and pyloroplasty. Grimson, Rowe, and Taylor (1952) have made a similar grouping but add this comment : "Of the three types of drainage procedure used pyloroplasty was frequently followed by delayed emptying of the stomach, exclusion by rapid emptying of the stomach with occurrence of the dumping syndrome, and the short-loop gastro-enterostomy gave best results." Orr and Daintree Johnson (1949) whilst currently combining vagotomy with hemigastrectomy, report "despite our earlier fears, gastro-enterostomy plus vagotomy has continued to give excellent results in the small group in which it has been used". The paper published by Hoerr and his associates from the Cleveland Clinic (Hoerr, Brown, Rumsey and Crile, 1952) gives a comprehensive report on the results of vagotomy and gastrojejunostomy. Their mortality was 0·5 per cent; 90 per cent of the patients have ended up with a satisfactory clinical result, and they conclude that the good clinical results warrant further employment of this form of treatment. Their results are very similar to our own, except that they have encountered a higher percentage of stomal ulceration. A second and larger group of cases is reported in the 1952 report of the peptic ulcer committee of the American Gastro-enterological Association, details of which will be quoted later. When analysed this report shows that vagotomy and gastrojejunostomy compare favourably with all other surgical procedures except in regard to the incidence of ulcer symptoms after operation. There is a strange contradiction in the details of two tables in the report, one of which gives the incidence of ulcer symptoms after vagotomy and gastro-enterostomy as 6 per cent whilst in the other table it is given as 28·3 per cent. Unless the second figure is the correct one it is difficult to understand how the Committee has arrived at its published conclusion that the results following gastric resection

alone were superior to those following vagotomy and gastro-enterostomy.*

The results of the treatment of duodenal ulcer by gastric resection are somewhat uncertain. A limited resection of stomach is apt to be followed by an unduly high incidence of stomal ulceration. After an extensive resection there is a tendency to malnutrition, anæmia, loss of energy, and a variety of digestive disturbances. The mortality of the operation varies from a very low figure, less than 1 per cent in expert hands, to an unknown figure in inexperienced hands. Many writers draw attention to a high incidence of digestive disturbances after gastrectomy. They are listed as cases of ' dumping ', hypoglycæmia, or post-cibal symptoms. On the other hand some authors report over 90 per cent of their patients to be well or improved following gastrectomy. Evidence that all is not perfect in the gastrectomy field is provided by the number of surgeons who now combine vagotomy with gastrectomy. The report of the American Gastro-enterological Association is based on a cross-section of reports from 72 hospitals, and the results must be rightly regarded as a good average of those obtainable. Their results are subdivided according to whether or not there was a history of hæmorrhage before operation. Since the group in which there was a history of hæmorrhage includes a number of emergency gastrectomies, it seems only fair to compare our results with the group in which there was no history of hæmorrhage. This has been done in *Table IX*.

Table IX.—Comparison of Results

Report of American Gastro-enterological Association

	Recurrence by X-ray	Hæmorrhage in follow-up	Ability to work	Free of ulcer symptoms	Mortality	Other abdominal distress
	per cent	per cent	per cent	per cent	per cent	per cent
Gastric resection: Less than 70 per cent resected	2·0	6·3	90·5	94·1	3·29	21·3
More than 70 per cent resected	1·3	1·3	92·8	96·7	1·76	12·8
Vagotomy and gastric resection	1·3	1·3	77·8	96·8	2·2	34·4
Vagotomy and gastro-enterostomy	2·4	2·1	94·8	(93·7) (71·7)	1·4	20·2
Results of Cases summarized from this Paper						
Vagotomy and gastro-jejunostomy	(Proved by operation) 1·0	2·0	97·5	98·0	0·5	20·0

When it is remembered that all our cases have been followed up for at least three years and include a considerable percentage of patients with a history of hæmorrhage before operation, there can be no doubt that vagotomy and gastrojejunostomy is a treatment of duodenal ulcer which bears comparison with any other method of treatment.

CONCLUSION

The results of the treatment of duodenal ulcer by vagotomy and gastrojejunostomy suggest that it is a method worthy of serious consideration. It has a low mortality, an absence of serious post-operative complications, and a high proportion of satisfactory results. Our results support the opinions of an increasing number of surgeons who recommend this treatment for duodenal ulcer.

*Subdiaphragmatic Vagotomy and Gastro-enterostomy (*Gastro-enterology*, 1952, **22**)

		Free of ulcer Symptoms	*Not free*
Part I, Table 26 p. 335	Without hæmorrhage	460 (93·7 per cent)	31 (6 per cent)
	With hæmorrhage	182 (96· 8 per cent)	6 (2·9 per cent)
Part III, Table 3 p. 463	Without hæmorrhage	460 (71·7 per cent)	182 (28·3 per cent)
	With hæmorrhage	31 (83·8 per cent)	6 (16·2 per cent)

There seem to have been some interposition of the numbers 182 and 31, producing a considerable alteration in the percentage free of ulcer symptoms.

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DIVERTICULUM OF THE DUODENUM

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DIVERTICULUM of the duodenum is a fairly common incidental finding (2 per cent) in barium-meal examinations, but few are found in the rest of the small intestine. In the case described below, the diverticulum was of unusual size, situated in the fourth part, and was tender on direct palpation during fluoroscopy.

CASE REPORT

The patient, a male aged 61, had had symptoms typical of a chronic duodenal ulcer for twelve years. In 1949 a barium meal performed elsewhere showed a duodenal ulcer. In 1953 he had hæmatemesis and melæna treated at home. A barium meal in March, 1954, showed a normal stomach and duodenal cap, with no evidence of old or recent ulceration, but there was a substantial, tender diverticulum on the inner border of the fourth part of the duodenum (*Fig.* 636).

Recurrence of peptic ulceration was excluded as the cause of his symptoms. On March 16 diverticulectomy was undertaken by Sir Cecil Wakeley. The proximal duodenum showed no evidence of past or present disease, but hidden in the extraperitoneal tissues, at the lower border of the pancreas, and lying to the left of the superior mesenteric vessels below the root of the transverse mesocolon, was the diverticulum. It was about ¾ in. in diameter, and was thin-walled. It was not embedded in actual pancreatic glandular tissue, nor was there any evidence of pancreatitis. The diverticulum was separated by blunt dissection, and removed after ligation of the narrow neck. Inversion was not thought to be desirable on account of its size. The stump was then buried under a few interrupted sutures, picking up the neighbouring bowel wall.

For the first post-operative week the patient was fed by intravenous drip, and a long duodenal tube with its tip beyond the duodenum. No difficulties or complications ensued.

Histological section showed the diverticulum to be of the acquired type, with muscularis mucosa being the only muscle in its wall. The mucosa showed intense plasma-cell infiltration, but no ulceration.

COMMENT

Duodenal diverticulum is a not uncommon finding, but only 23 per cent (Edwards, 1939) are in the third or fourth parts. Operation is indicated on account of (*a*) large size, (*b*) stasis, and (*c*) persistent symptoms when other causes have been excluded. In this case there was little doubt that the diverticulum was the cause of the symptoms, as evidenced by tenderness on direct pressure during the barium-meal examination. Spriggs and Marxer (1925) could ascribe symptoms to 18 out of 38 cases of duodenal diverticulum, and of these only 2 had had bleeding. In the case reported by Rowlands and King (1954) the diverticulum was in a similar situation to that now described, but a definite duodeno-aortic fistula, the result of ulceration in the diverticulum, was demonstrated as the cause of bleeding.

FIG. 636.—Radiograph showing large diverticulum in fourth part of duodenum.

In the case described, both hæmatemesis and melæna had occurred, which can only be presumed to have arisen in the diverticulum.

I should like to thank Sir Cecil Wakeley for allowing me to publish this case.

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THE GASTRO-ŒSOPHAGEAL 'SPHINCTER' AND THE MECHANISM OF REGURGITATION

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In 1719 Helvetius wrote a description of a morphological sphincter at the cardio-œsophageal junction and so started a controversy which has continued to the present day. The persisting division of modern anatomical opinion is illustrated by the reports of Lendrum (1937), who dissected 150 œsophagi and denies that a sphincter exists, and of Lerche (1950) who studied 100 specimens and is convinced that the structure described by Helvetius is an anatomical fact. Amongst those who believe in the presence of an inherent sphincter are Hurst (1911), Farsell (1912), and Abel (1929), but even they do not agree on its exact site. Other workers, unimpressed by the evidence for an intrinsic sphincter, have looked elsewhere for a mechanism which would explain the sphincteric properties of the cardia. Chevalier Jackson (1922) claimed that the diaphragm exerts a pinch-cock effect on the œsophagus and this view has been widely accepted. Dick and Hurst (1942) and Negus (1946) support the belief that the œsophagus enters the stomach in such a manner as to form a flap-valve between its left lip and the fundus. Finally, Payne and Poulton (1927) have suggested that the lower end of the œsophagus possesses sphincteric action even though no distinct morphological structure can be displayed.

The controversy has arisen because of the need to account for the functions of the cardio-œsophageal junction in limiting regurgitation and delaying the entry of œsophageal contents into the stomach. The problem also concerns the clinician who is interested because of the syndromes which result from disorder of these functions. In the early years of this century attention was particularly directed towards the disorder of emptying which resulted in dilatation and elongation of the gullet. The theories of spasm (cardiospasm) and failure of relaxation (achalasia) were expounded and these in turn started their controversies. During the past decade a great deal has been said and written about gastro-œsophageal regurgitation. Arising largely from the influence of Allison, the importance of sliding hiatus hernia in causing œsophagitis, through acid-regurgitation, has become generally known and the clinical recognition of the condition is now commonplace.

It is the purpose of this essay to report certain experimental and clinical observations which cast some light on the cardio-œsophageal mechanism. True to the current trend, this work is chiefly concerned with regurgitation, particularly regurgitation in the absence of gross pathological abnormality.

THE MECHANISM OF DELAY AT THE CARDIO-ŒSOPHAGEAL JUNCTION

Physiological Delay.—Under normal conditions swallowed food may be temporarily arrested at the lower end of the œsophagus. When a succession of swallowing efforts are made the food tends to pass continuously into the stomach, but at the completion of the swallow a residue remains in the lower œsophagus to be propelled onwards by the secondary contraction waves. During barium examination it can be noted that the opaque medium enters the stomach most readily during expiration,

FIG. 637.—Illustration of technique used to produce a controlled increase in the intraperitoneal pressure. This picture demonstrates the position of the subject on the screening table, the site of the inflatable balloon, and the method of assembling the equipment. The patient is lying on a large bath towel which is then wrapped tightly around the abdomen and fixed with five large safety-pins.

whilst on deep inspiration the secondary peristaltic waves may fail to force the barium into the stomach. In these circumstances the contraction wave is seen to approach within a few centimetres of the cardia, and the terminal œsophagus, caught between a resisting force from below and a distending force from above, dilates to form the phrenic ampulla. Identical appearances can be produced when the Valsalva test is performed. These observations have been said to prove that contraction of the muscular crura of the diaphragm constricts the œsophagus. An alternative suggestion is that the pressure differences between thorax and abdomen are the cause of the delay.

Throughout normal quiet respiration the intrathoracic pressures are negative, varying from minus 5 cm. water on expiration to minus 10 cm. water on inspiration, whilst intraperitoneal pressures range from zero on expiration to a positive pressure of 5 cm. of water on inspiration. These pressures are directly transmitted to the œsophagus (Dornhorst and Leathart, 1952) and stomach (Cannon, 1922) and so produce a pressure gradient of at least 5 to 15 cm. of water across the gastro-œsophageal junction. Such a resistance could well account for the physiological delay of the passage of food into the stomach. The following experiments were carried out in order to test the validity of this view.

* This essay by Paul Marchand, who is now in the Department of Surgery, University of Witwatersrand, Johannesburg, won the Moynihan Prize awarded by the Association of Surgeons of Great Britain and Ireland in 1954.

Corrigenda :—

p. 504, left-hand column, lines 11, 12 :—
for " Farsell (1912) " *read* " Forssell (1923) ".

p. 504, right-hand column, 7 lines from bottom :—
for " (Cannon, 1922) " *read* " (Cannon, 1911) ".

p. 507, right-hand column, 4 lines from bottom :—
for " Johnstone " *read* " Johnstone (1946) ".

p. 509, right-hand column, line 15 :—
for " (Cannon, 1922) " *read* " (Cannon, 1911) ".

Technique.—The principle of the experiment is gradually to increase the intraperitoneal pressure and to observe the effect this has on the radioscopic appearances of the barium-filled œsophagus.

The intraperitoneal pressure can be controlled by securing a rubber balloon against the abdomen with an encircling body bandage extending from pelvis to chest. The balloon is inflated by means of a sphygmomanometer hand-pump and the pressure within the balloon is registered on a mercury manometer (*Fig.* 637). On several occasions it has been possible to perform the experiment on patients with a therapeutic pneumoperitoneum so as to correlate the abdominal balloon pressures with the intraperitoneal pressures. On these occasions it has been shown that there is a direct linear relationship between the balloon and the intraperitoneal pressures (*Fig.* 638).

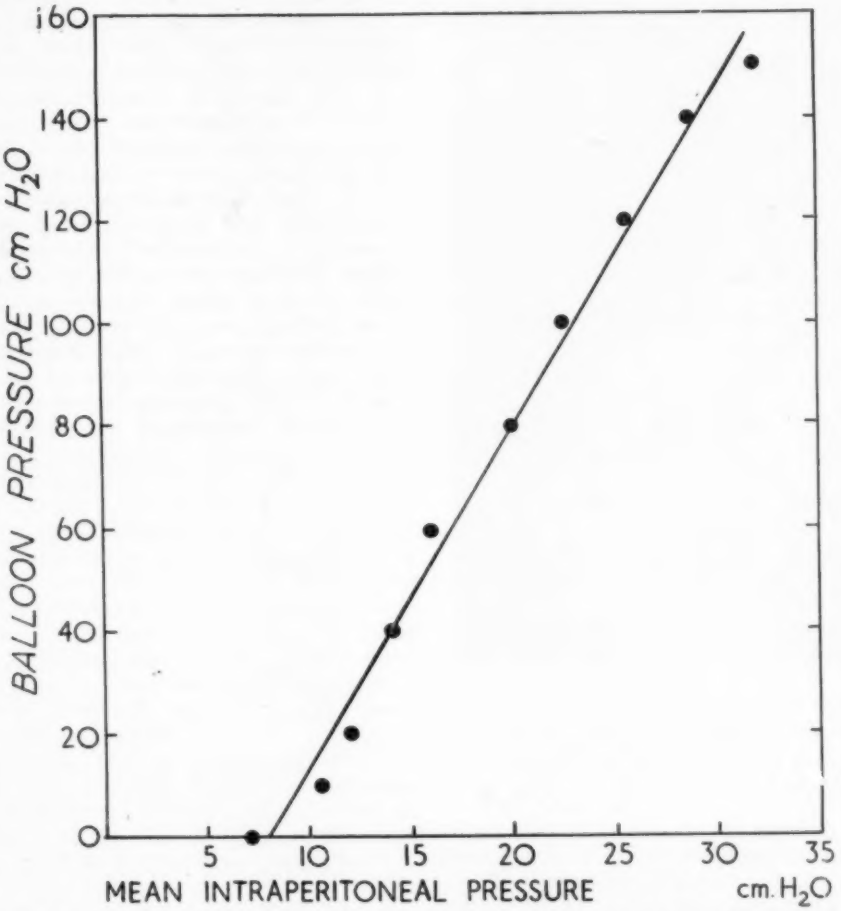


FIG. 638.—Correlation of balloon pressures with mean intraperitoneal pressures. The peritoneal pressures were measured by inserting a needle into a pneumoperitoneal space and recordings were taken each time the balloon pressure was increased by 20 cm. of water.

Observations.—

1. A phrenic ampulla is always produced when barium is swallowed with the balloon inflated to a pressure of 60–80 cm. of water. This will happen with a relaxed subject and the absence of diaphragmatic contraction can be confirmed by the high position of the diaphragm (*Fig.* 639).

2. Increasing the pressure in the balloon to above 120 cm. of water may prevent the passage of barium into the stomach or else the œsophagus will empty only after vigorous peristaltic contractions have been evoked.

3. When swallowing efforts are made against high intraperitoneal pressures regurgitation from the stomach may occur and newly swallowed barium may be forced back into the mouth.

4. The subjects frequently complain of dysphagia when attempting to swallow against high intraperitoneal pressures.

Except for the high position of the diaphragm, the fluoroscopic appearances produced when barium is swallowed against an artificially raised intraperitoneal pressure are identical with those observed when the Valsalva manœuvre is performed by the same subjects. Before suggesting that the effects on the œsophagus are produced by the increased pleuroperitoneal pressure gradient, it is necessary to show that this gradient is indeed increased during the manœuvre. Straining against the closed glottis will raise both intrapleural and intraperitoneal pressures, and if they rise equally then pressure differences cannot be implicated. Opportunities to correlate the intrapleural and intraperitoneal pressures were afforded by two patients treated for pulmonary tuberculosis by combined artificial pneumothorax and pneumoperitoneum without phrenic nerve crush.

Needles were inserted into both cavities and simultaneous pressure recordings were made whilst the patients performed the Valsalva manœuvre (*Fig.* 640).

No great effort was required to raise intrapleural pressures to between 25 and 30 cm. of water, and up to this level the pneumoperitoneal pressures

FIG. 639.—Radiograph taken whilst a patient was swallowing barium against a raised intraperitoneal pressure. The production of a phrenic ampulla is shown. The outline of the inflated balloon can be seen and the high position of the diaphragm indicates that it is relaxed and cannot therefore be constricting the œsophagus.

remained at an average of 10 cm. of water higher than the intrapleural pressures. On great exertion the peritoneal pressures increased much more rapidly than the pleural pressures. As far as can be judged, this accelerated increase in the intraperitoneal pressure (and it increases with great rapidity) coincides with the full forcible contraction of the abdominal muscles. It is difficult to persuade patients to perform the Valsalva manœuvre correctly, and it would seem that a successful result depends upon full muscular contraction supplementing the respiratory efforts. According to these observations, during a maximum straining effort the pressure gradient between the two cavities and presumably between the intra-œsophageal and intragastric pressures is between 30 and 40 cm. of water (*Fig.* 640). The difference in the pressures between the two cavities is obviously increased on deep inspiration, and it is suggested that both inspiration and the Valsalva test exert their delaying action upon œsophageal emptying by virtue of this effect. The alternative explanation of a pinch-cock action of the right crus of the diaphragm obstructing the œsophagus is discarded for the following reasons :—

1. Paralysis of the right phrenic nerve does not interfere with the delaying effect of deep inspiration or the Valsalva manœuvre.

2. When a finger is passed through the hiatus during operations in this region it is not possible to confirm a gripping action of the crura even when hyperventilation is induced by making the unconscious patient breathe 5 per cent carbon dioxide.

Abnormal Delay.—It is believed that the pleuroperitoneal pressure gradient accounts for the momentary physiological arrest in the passage of food from œsophagus into the stomach. It is difficult to explain prolonged pathological delay in this way, and a persistently raised pressure gradient sufficient to resist the force of normal œsophageal peristalsis cannot be demonstrated in these cases. Two conditions in which prolonged delay occurs at the level of the diaphragm have been encountered.

1. *Acute Caustic Soda Injury.*—During the past five years, 158 cases of caustic soda burns of the œsophagus have been investigated. Ninety-two of these patients were admitted to hospital within a few hours of injury and all had 'barium swallow' examinations soon afterwards. It came to be recognized that persistent delay of the opaque medium in the lower œsophagus denoted œsophageal involvement though not necessarily of grave severity. When the motor activity of the œsophagus was visibly

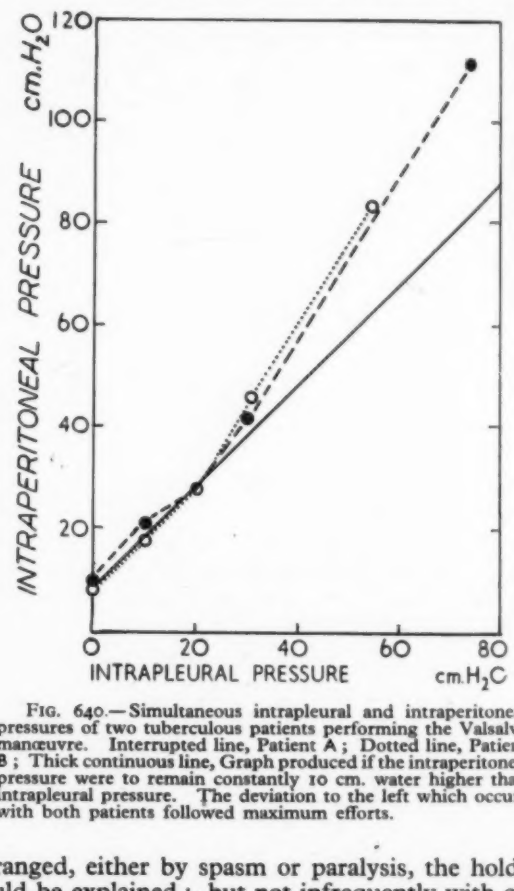


FIG. 640.—Simultaneous intrapleural and intraperitoneal pressures of two tuberculous patients performing the Valsalva manœuvre. Interrupted line, Patient A; Dotted line, Patient B; Thick continuous line, Graph produced if the intraperitoneal pressure were to remain constantly 10 cm. water higher than intrapleural pressure. The deviation to the left which occurs with both patients followed maximum efforts.

deranged, either by spasm or paralysis, the hold-up could be explained; but not infrequently with cases of relatively mild involvement no obvious motor disturbance could be seen. During examination in the erect position the barium would accumulate approximately to the level of the aortic arch (15–20 cm. above the diaphragm in an adult), and would then drip slowly into the stomach. Contraction

waves would descend to within a few centimetres of the cardia, but never quite seemed to reach it. These appearances are strongly reminiscent of the early stages of achalasia of the cardia, and suggest that the secondary contraction waves fail to propagate through a refractory segment in the terminal œsophagus. In support of this is the fact that, though the most severe lye strictures are usually produced below the level of the aorta, a segment of 1–2 cm. of the terminal œsophagus often escapes injury. It is as if the lumen of this segment remained occluded at the time of injury and did not come into contact with the corrosive (*Fig.* 641).

2. '*Achalasia of the Cardia.*'—The pleuroperitoneal pressure gradient is normal in cases of mega-œsophagus, yet there is a prolonged delay at the lower end of the œsophagus. At operation or necropsy a short segment of the terminal œsophagus is always in marked contrast to the thickened dilated part above. No evidence of muscle hypertrophy can be found, and the absence of any severe resistance at this site is confirmed by the œsophageal fluid level, which is almost always between 15 and 20 cm. above the diaphragm. This represents just sufficient hydrostatic pressure to overcome the pressure gradient across the diaphragm. Heller's operation, in which the muscle-fibres of this segment of the œsophagus are divided down to the mucosa, results in marked symptomatic improvement. If paralysis of the propulsive œsophageal musculature is the underlying cause, then this procedure should not cause improvement, as the pleuroperitoneal pressures remain unaltered. The fault does seem to be in the terminal œsophagus, and Hurst's explanation, that the muscle tone of terminal œsophagus fails to relax in the van of an oncoming peristaltic wave, would appear to be reasonable.

These two conditions provide some evidence for the belief that the terminal œsophagus possesses an inherent sphincteric function even though no anatomical sphincter can be displayed. Further evidence for this view will be presented later in this essay.

THE MECHANISM OF PREVENTION OF REGURGITATION

The pleuroperitoneal pressure gradient constantly tends to displace stomach contents into the œsophagus, yet continuous regurgitation is in some way prevented. Currently, there is common accord that this is mainly accomplished by the oblique entry of the œsophagus into the stomach which acts as a flap-valve when the stomach distends. Barrett (1952) and Donnelly (1953) are of the opinion that the right crus of the diaphragm compresses the terminal œsophagus on deep inspiration and so reinforces the resistance offered to regurgitation. Johnstone (1951) believes that a sphincter at the gastro-œsophageal junction aids in preventing reflux. Allison (1951), whilst considering the diaphragm to be important, agrees that an intrinsic mechanism contributes to continence of the cardia.

The Œsophago-gastric Junction.—Reflux of stomach contents occurs when the intragastric pressure rises above that which the cardia can withstand. It is virtually accepted that the angle of entry of the œsophagus into the stomach is of great importance in resisting this regurgitating force, and several experiments on young male cadavers were designed to confirm this belief.

The pylorus was cannulated and the stomach distended with water from a reservoir which was raised alongside a measured rule until the water was seen to escape from the œsophagus.

The experimental findings illustrated in *Fig.* 642 clearly confirm the importance of the mechanical

FIG. 641.—Radiograph showing the typical distribution of strictures following caustic injury of the œsophagus. The tubular stricture at the lower end stops short of the gastro-œsophageal junction and a terminal segment is normally distendable. This is a constant finding which suggests that spasm of this segment occurs at the moment of injury and so itself escapes corrosion, but in so doing causes severe injury to occur immediately above.

arrangement of the fundus which, when excluded from the rest of the stomach (*Fig.* 642 B), diminishes threefold the resistance offered by the cardia to regurgitation.

When the left leaf of the diaphragm is removed to allow the fundus to bulge upwards without hindrance, the pressure necessary to induce regurgitation is increased by half again (*Fig.* 642 C).

The liver tunnel, the crura, and the pressure of surrounding organs are important in maintaining the relative positions of the stomach and œsophagus and the efficiency of the cardio-œsophageal angle (*Fig.* 642 D).

The Intrinsic Sphincter.—During barium examination of a patient with hiatal hernia it is often possible to demonstrate a weak barrier to regurgitation from the intrathoracic stomach. Johnstone believes that this is evidence for an intrinsic sphincter at the cardio-œsophageal junction. Further support for this view was obtained during this investigation.

Twenty normal young adults were subjected to abdominal compression in the head-down position. The stomach was filled by drinking watery barium and the balloon was then gradually inflated until regurgitation was seen or until a pressure of 150 cm. of water was reached. This is about as much compression as is comfortably tolerated and therefore attempts to produce regurgitation with higher pressures were thought to be inadvisable.

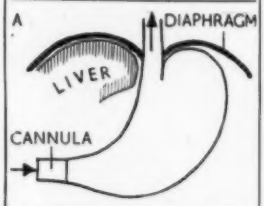
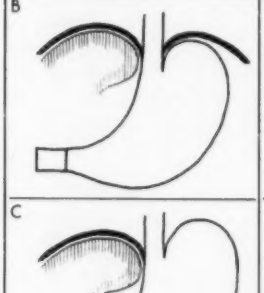
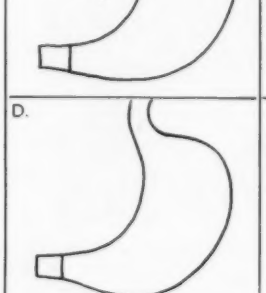
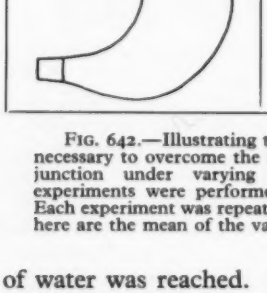
Illustration of Experiment	Description of Experiment	Pressure Producing Reflux
A 	Control. Pylorus cannulated. Rest of stomach left undisturbed.	28 cm. of water
B 	Clamp placed across stomach from left lip of œsophago-gastric junction to greater curve so as to exclude the fundus from the rest of the stomach.	9 cm. of water
C 	Left leaf of diaphragm removed and abdominal wall left open. Distension of the stomach was thus unhindered and it was able to bulge up into the chest and forwards.	42 cm. of water
D. 	Œsophago-gast. angle abolished by freeing terminal portion and removing the liver and the right diaphragm. The terminal œsophagus is displaced to right.	3 cm. of water

Fig. 642.—Illustrating the retrograde pressures which were necessary to overcome the resistance of the cardio-œsophageal junction under varying experimental conditions. These experiments were performed on young adult male cadavers. Each experiment was repeated three times and the results given here are the mean of the values obtained.

The results of these experiments were so variable that no purpose is served by tabulating them. However, certain observations were made which were instructive :—

1. The higher the pressure at which reflux was produced, the more forcible was regurgitation. For instance, pressures of 60 cm. of water seldom caused barium to regurgitate into the cervical œsophagus, whilst pressures of 150 cm. of water usually did so and frequently forced the barium into the mouth.

2. A striking observation was made by chance when a person who had failed to regurgitate at the maximum pressure was given some extra barium to swallow whilst the balloon was still inflated. At the very instant of swallowing, the barium already in the stomach was seen to regurgitate so powerfully that it forced the barium that had just been swallowed back into the mouth. This observation has often been confirmed since.

3. Regurgitation is sometimes seen when an œsophageal peristaltic wave reaches the cardia. This observation was reported by Johnstone (1951) and is to be distinguished from the reflux which occurs at the inception of a swallowing effort.

These observations illustrate two points which are fundamentally important in producing regurgitation :—

1. The force which causes regurgitation is the intragastric pressure.

2. The structural arrangement of the œsophago-gastric junction is reinforced by some active mechanism which can be inhibited by swallowing.

Conclusions.—Physiological delay to the passage of food from the œsophagus into the stomach occurs on deep inspiration and during the Valsalva test. This can be accounted for by differences in pressure between the thoracic and abdominal cavities, and is probably incidental to the anatomical situation of the œsophagus. This delay is never more than temporary, as physiological pressure differences sufficient to resist the force of an œsophageal peristaltic wave cannot be long maintained.

The pathological delay of 'achalasia of the cardia' and mild cases of acute caustic injury would appear to be due to a different mechanism. It is believed that Hurst's hypothesis of a failure of relaxation of the terminal œsophagus provides a reasonable explanation for the delay.

Regurgitation from stomach into œsophagus would be continuous if there were not some arrangement to resist the force of the intraperitoneal pressure. The oblique entrance of the œsophagus into the stomach is most important in this respect and it is believed that this is reinforced by the resting muscle tone of the terminal œsophagus, which maintains a closed lumen at the junction of œsophagus and stomach. The tonic closure of the œsophagogastric junction is inhibited by swallowing and by the arrival of a peristaltic wave at the lower œsophagus. If the intragastric pressure is high, the resisting mechanism may be sufficiently weakened at the moment of swallowing to permit regurgitation to occur.

An anatomical study has not been undertaken, but in view of the historical disagreement on the subject it can safely be assumed that no very obvious sphincter is to be found in the lower œsophagus. This is not necessarily an objection to the view here presented, for Meyer and Schmidt (1930) and Schindler and Dailey (1941) have put forward strong evidence to show that typical sphincter activity may be found in parts of gut which are remote from anatomical sphincters.

It is contended that the diaphragm cannot constrict the terminal œsophagus, and that it plays no part in preventing regurgitation. This view has arisen partly because the resistance in the œsophagus is at the level of the diaphragm. This is accounted for by the fact that the diaphragm is the boundary between the cœlomic cavities and effects which depend on pressure difference will therefore be exerted at this precise level.

GASTRO-ŒSOPHAGEAL REGURGITATION

The Mechanism of Regurgitation.—Theoretically, regurgitation could be due to one of three basic causes :—

1. Increase of the intragastric pressure above levels normally withstood by the resisting mechanism.
2. Loss of the normal œsophago-gastric angle.
3. Inhibition of the tone of the terminal œsophagus.

1. *Increase of Intragastric Pressure.*—It has been thought that with a normal stomach, the greater the gastric pressure the firmer the closure of the œsophago-gastric 'flap-valve'. An increase in pressure alone should not therefore be a cause of regurgitation. That this is untrue is proved by those cases where regurgitation could be induced simply by elevating the intraperitoneal pressure. Donnelly (1953) considers that deep inspiration lessens the efficiency of the 'flap-valve' because the descent of the left leaf of the diaphragm depresses the fundus of the stomach and alters the œsophago-gastric angle. This, or other causes of weakening of the cardia may well be commonly present, but it is certain that sudden increase in the intragastric pressure is often the predominant factor in causing regurgitation. Increase of the intragastric pressure may be active or passive.

Passive regurgitation: Cannon (1911) has shown that the stomach, like the bladder, accommodates for its increasing contents by reflex relaxation of its muscular walls, so that excessive pressure rise is prevented. However, considerable, sharp elevation in tension is caused by postural changes such as stooping, bending forwards, or lying supine. The degree of such movement necessary to cause an increase in pressure varies indirectly with the degree of gastric distension. The tension within a distended stomach is subject to violent increase with slight but appropriate body movements.

The importance of gastric distension is easily confirmed by a simple experiment. A subject is given graduated amounts of watery barium to swallow against a constant abdominal compression force (by means of the balloon technique) of 120 cm. of water and the effects are viewed by radioscopy. In a series of 10 young adults, no one regurgitated after 500 ml. had been swallowed, 3 regurgitated after 1000 ml., and 5 others after 1500 ml. had been taken.

Intraperitoneal pressures are passively transmitted to the stomach and when the peritoneal capacity is decreased as in pregnancy or adiposity slight postural changes seem to cause an inordinate rise in the intragastric tension. Similarly, contraction of the diaphragm and abdominal muscles, particularly in the presence of gastric distension, is capable of raising the intragastric pressure.

Where extrinsic factors are the sole cause for the high gastric tension, the act of regurgitation is immediately effective in reducing that pressure and regurgitation stops. Passive regurgitation is therefore self-limiting, though it may be rapidly repeated, for the contents forced into the œsophagus may be immediately returned into the stomach by reactive œsophageal peristalsis.

Active regurgitation: Gastric contractions can also cause a sharp increase in the intragastric pressure particularly if the stomach is distended. Normally it is the empty stomach which is the most active, whereas the full stomach is usually at rest (Alvarez, 1948). When gastric contractions are associated with pyloric closure the intragastric pressure may rise violently and cause regurgitation. This is what happens during vomiting. It has been shown that vomiting is a highly complex reflex involving spasmodic contraction of the muscles of expiration, particularly of the diaphragm and abdominal musculature. This passively increases the intragastric pressure, which in addition is actively increased by spasmodic contraction of the middle and lower thirds of the body of the stomach associated with spasm of the pyloric outlet (Cannon, 1922). Reversed peristalsis, starting at the pylorus, may also occur. The reflux of vomiting lasts as long as the stomach contains material which can be regurgitated.

Vomiting and postural regurgitation can be clearly differentiated on clinical and mechanical grounds, yet between the two extremes are gradations of regurgitation which are impossible to differentiate. Particular difficulty is experienced in assessing the quality of regurgitation seen in infants and young children, probably because both causes may operate at the same time. In the remainder of this essay the discussion is limited to intermittent gastro-œsophageal reflux seen in adults, without nausea and predominantly in response to passive increase in the intragastric pressure.

2. *Alteration of the Normal Œsophago-gastric Angle.*—Disruption of the normal œsophago-gastric angle occurs classically in sliding hiatus hernia. In this condition the cardia is displaced upwards into the chest and the normal anatomical angle is abolished. The tonic contraction of the terminal œsophagus still provides a weak defence and an increase in gastric tension following postural change is usually necessary to cause regurgitation. The tonic closure of the terminal œsophagus seems just capable of withstanding the normal pleuroperitoneal pressure gradient. Strong proof that the altered angle is the factor of paramount importance is that with a para-œsophageal hernia, in which the œsophago-gastric junction is undisturbed, reflux does not occur.

3. *Inhibition of Tone of the Terminal Œsophagus.*—The resting tonic contraction of the terminal œsophagus can be inhibited by swallowing. This inhibition occurs either simultaneously with the gulping action or some 4 seconds later, when the wave of relaxation, preceding the secondary contraction waves, reaches the terminal œsophagus. If the intragastric pressure is sufficiently high at these instants, regurgitation will occur.

If this is correct then regurgitation should occur at meal times, for the stomach is distended, swallowing is frequent, and the body is in an attitude which tends to cause an increase in the gastric pressure. That this is indeed so was proved by 4 cases of perforated œsophagus treated in the Thoracic Unit. Two were caustic strictures perforated at the junction of middle and lower thirds of the œsophagus during antegrade dilatation, and 2 were carcinomatous structures perforated whilst introducing a Souttar's tube. In all cases the cardio-œosophageal junctions were intact, the fistulas being well above this level

and passing into the right pleural sac. All were treated by immediate gastrostomy and intercostal drainage (a technique not necessarily advised for rupture of a comparatively healthy œsophagus). The great disadvantage of this treatment is that considerable amounts of the gastrostomy feeds are lost through the pleural drains, showing that regurgitation, to at least mid-œsophagus level, occurs. It is difficult for patients to stop their involuntary swallowing efforts during gastrostomy feeding, but the loss can be reduced to a minimum by administering frequent small feeds with the patient lying on one or other side and remaining so for about an hour afterwards.

Symptoms of Passive Regurgitation.—The regurgitation which occurs regularly during and after meals is seldom sensed and the occasional belch passes unnoticed. It is only when reflux becomes persistent that symptoms obtrude themselves upon our consciousness. The three cardinal symptoms are flatulence, postural regurgitation, and pain.

1. *Flatulence.*—In the erect position the œsophagus may open into the gastric air-bubble and should regurgitation occur only gas is expelled. It depends on the force of regurgitation and the strength of the reactive œsophageal peristalsis whether the bubble of gas is forced into the mouth as a belch or returned to the stomach. When the bubble of air lies in the œsophagus it is often sensed and can then be voluntarily expelled by contracting the abdominal muscles and straining against the closed glottis to increase the abdominal and pleural pressures. This same action can cause regurgitation from a distended stomach particularly if preceded by a swallow or a gulp to inhibit the lower œsophagus. This is one of the ways in which an adept can perform a voluntary belch.

2. *Fluid Regurgitation* (*Water-brash*).—If regurgitation occurs at the moment of bending well forwards or whilst lying down then it will be the fluid content which escapes from the stomach. If the force of regurgitation is sufficiently great to overcome the reactive œsophageal contraction and closure of the cricopharyngeus sphincter then the fluid will enter the mouth. The taste of this fluid will depend entirely on the nature of the gastric contents; it may be watery, sour, or burning, or it may taste of recently ingested food. In certain postures both air and fluid may be regurgitated simultaneously or a belch may be followed by the regurgitation of fluid, and then the term 'acid-eructations' may be applied.

3. *Pains.*—Violent regurgitation may produce a sensation which is variously described by different people, but is always uncomfortable, often painful, and sometimes distressing. Jones (1938) attempted to evaluate the nature of the pain which follows œsophageal distension and found that a sensation of choking, of fullness, of pressure, or of burning was produced, the differences depending partly on the force of distension and partly on the level of the œsophagus affected. He found that pain caused by distension of the upper œsophagus was well localized and generally described as choking or as a feeling of pressure, whereas in the lower œsophagus the usual description was of an ill-defined substernal burning sensation.

The choking, boring pains of œsophageal distension or spasm have occasionally been produced during regurgitation experiments. Pain is not felt when barium regurgitates promptly into the mouth or when it is rapidly returned to the stomach. It occurs when the swallowed barium, on meeting the regurgitating barium, causes distension of the œsophagus and when the two forces are so balanced that the distension persists for some time. On one occasion the pain lasted for more than a minute and passed off only when the abdominal balloon was deflated. During all this time the distension at the meeting point of the two barium columns could be seen moving up and down for a few centimetres in the mid-œsophagus. The pain was usually described as choking or boring and was felt in the front of the chest or neck, vaguely in the midline and occasionally would radiate widely. Evans (1952) has shown that œsophageal pain, following gastro-œsophageal regurgitation, may be identical in distribution with the pain of angina pectoris. It is uncertain whether this type of œsophageal pain is due to distension (Jones, 1938) or spasm (Johnstone, 1951).

A sensation of burning can also arise from the œsophagus. Alvarez (1948) has pointed out that after swallowing a strong liqueur such as Cointreau, a burning sensation may be felt progressing down the œsophagus. All patients who swallow caustic soda complain bitterly of a burning cervical and substernal pain and though with overwhelming injury 'burning' may be a euphemistic term, there are mild cases where the only outcome is a severe and prolonged attack of 'heartburn'. Also during a dyspeptic attack associated with 'heartburn' the discomfort may be sensed rising upwards until a mouthful of bitter fluid is regurgitated. On occasions a swallow may succeed in reversing the burn and it is then felt to subside into the stomach. A burning substernal discomfort is frequently associated with gastro-œsophageal regurgitation, but there is nothing specific about this relationship. The discomfort is in the first place due to surface irritation of the œsophageal mucosa and this may be caused by any irritant if sufficiently concentrated and applied for a sufficiently long time.

The Causes of Symptomatic Gastro-œsophageal Regurgitation.—During the past five years, 19 patients have been investigated because of severe symptoms of regurgitation. These people had been provisionally diagnosed as having hiatus hernias, and indeed this was found in 12 of them. This series is far too small to draw any statistical conclusions as to the incidence of hiatus hernia amongst people with symptoms of regurgitation and no attempt has been made to do so. However, 'heartburn' is a very common complaint, and many people, including medical colleagues, have been questioned about this. The total material on which the following brief descriptions are based comprises :—

a. Nineteen adult patients referred to the Thoracic Unit with a provisional diagnosis of hiatus hernia.

b. Records of 22 doctors who have experienced symptoms of regurgitation.

c. Two hundred and fifty women questioned within a week of parturition.

Owing to the nature of the clinical material, this survey was as much an investigation of 'heartburn' as it was of gastro-œsophageal regurgitation. In the great majority of the people questioned the burning substernal discomfort or pain was the predominant symptom, but the presence of flatulence or postural regurgitation usually left no doubt as to the cause.

The term 'heartburn' is now established in everyday language and provided it is realized that it merely describes the predominant symptom of gastro-œsophageal regurgitation, there seems no reason for discarding it. The following list of the causes of regurgitation could equally well be termed the causes of heartburn.

1. *Occasional Reflux Dyspepsia.*—Most people suffer from occasional attacks of reflux dyspepsia and these follow dietary indiscretions or may be caused by a particular food which habitually disagrees with that person. Twice-cooked meats, acid wines, highly seasoned meals, dry toast, and many other types of food may be responsible.

These dyspeptic attacks are usually heralded by flatulence, which may start within a half-hour of ingesting the offending food. Other symptoms may never develop or regurgitation of small amounts of stomach contents may follow and, later, heartburn may be experienced. It is unusual for heartburn to begin less than an hour after taking the responsible substance and often two hours will pass before discomfort begins. Attacks may be precipitated by maintaining a bent posture for some time, and driving a car, gardening, and writing at a desk soon after meals are particularly responsible. Exacerbations of symptoms are due to recurrent regurgitation and these are frequently unrelated to posture. Sometimes the sufferer is standing bolt upright when an exacerbation occurs which suggests that during attacks the intragastric pressure is constantly raised. During attacks the stooping posture is often consciously avoided.

Heartburn is the predominant symptom of reflux dyspepsia and may occur in the absence of other evidence of regurgitation. The discomfort varies in site and intensity. It may be sensed rising upwards from the epigastrium into the neck to culminate in the regurgitation of a little acid-tasting fluid, or it may shift down in response to a swallow. Uncomplicated heartburn is not associated with dysphagia though the passage of food, particularly if irritant, may intensify the discomfort. Most attacks are improved or arrested, though often only temporarily, by antacids.

The underlying cause for the gastro-œsophageal reflux is obscure. It is possible that the offending substances produce gastric irritation and this causes pyloric spasm. During the few attacks which have been investigated by barium meals, delay in emptying has been prolonged and it may be that pyloric spasm causes the intragastric pressure to be unduly responsive to those intrinsic and extrinsic factors which affect it.

2. *Adiposity.*—Fat people are often liable to attacks of reflux dyspepsia. This particularly applies when the increase in weight is rapid and these people often suffer after every meal. The only method which will reliably prevent this tendency to dyspepsia is to embark on a stringent weight-reducing diet.

Deposition of fat in the omentum and abdominal viscera decreases the peritoneal capacity and it is probable that alterations of posture then have an excessive effect on the intragastric pressure.

3. *Cholecystitis and Duodenal Ulcer.*—Two people had such severe symptoms of regurgitation that they were at first thought to have hiatus hernias. After investigation one was found to have a duodenal ulcer and the other multiple gall-stones. No doubt other gastro-intestinal abnormalities will on occasions produce symptoms of reflux dyspepsia.

With both present cases it was possible to demonstrate gastro-œsophageal regurgitation by abdominal compression and to confirm that the reflux was the cause of the dyspeptic symptoms. In both cases symptomatic cure followed surgical treatment of the underlying condition.

4. *Air-swallowing.*—Excessive air-swallowing is said to be a neurotic manifestation and the heartburn which accompanies it has often been labelled a functional symptom. It is unfair to label all air-swallowers as neurotics as most dyspeptics are addicted because the habit affords them some relief. Gastric distension can cause considerable discomfort and it is not uncommon to see a person who has dined too well gulping air prior to emitting a satisfying belch. In such cases the swallow is made so as to facilitate gastro-œsophageal reflux, which in turn causes an immediate though usually temporary decrease in the intragastric pressure. This may be the start of habitual air-swallowing, which, when established, may produce a vicious circle. The stomach becomes distended with air and this causes discomfort, which in turn stimulates an urge to swallow in order to obtain relief through regurgitation. In these people the stomach may become grossly distended with air and the regurgitant material is usually gaseous, though a little unbuffered gastric juice may be included. In these cases acid eructation is the prominent symptom and the condition is one of 'flatulent dyspepsia'.

5. *Pregnancy.*—The 250 women who were interviewed within a week of delivery were the unselected consecutive admissions to a large maternity unit. They were all questioned about symptoms of heartburn during their recent pregnancy, but only 14 were examined radiologically.

It was found that 182 (70 per cent) of the women experienced heartburn during the pregnancy for which they were in hospital. Only 3 confessed to being troubled by heartburn (except very occasionally) when not pregnant. The discomfort was seldom sufficiently severe to interfere with the daily routine and most of the women considered it to be a normal accompaniment of pregnancy.

In the great majority of cases the discomfort began after the fifth month, though in 16 (9 per cent) it started as early as the second month, of pregnancy. The dyspepsia usually got worse as the uterus enlarged, but there were 4 patients whose heartburn ended before the sixth month had passed. On the whole it seems as if the regurgitation increases as the capacity of the upper abdomen diminishes. In support of this it was interesting to note that 20 (25 per cent) of the 78 primigravida who experienced

heartburn were relieved during the final month of their pregnancy. This may be related to descent of the uterus due to engagement of the fœtal head, and this results in a greater capacity of the upper abdomen. Amongst the multipara, who do not usually experience lightening in the last month, less than 10 per cent (10 cases out of 104) experienced similar improvement. In every case all symptoms ceased after parturition.

In most instances a typical postural history was obtained, the discomfort being produced by polishing floors, gardening, lacing shoes, and, most frequently, lying down at night. Ninety-three (50 per cent) had sufficient discomfort for them to take a regular antidote. In most cases an antacid such as bismuth, McLean's powders, Rennie's tablets, or soda bicarbonate sufficed to produce temporary improvement. Soda-water, hot water, and peppermint also had their advocates.

Fourteen patients who had suffered from severe regurgitation symptoms consented to barium examinations with abdominal compression. These were done between 3 and 6 weeks after parturition. Dutton and Bland (1953) recently reported 9 cases of hiatal hernia complicating pregnancy, but no hernia was found amongst the present cases.

As a result of this survey it would seem that the dyspepsia of pregnancy does not differ from that which is known to result from gastro-œsophageal reflux. The symptoms are heartburn, flatulence, and postural regurgitation, and though heartburn usually predominates, cases are seen where flatulence or postural regurgitation may occur without pain or discomfort. It is believed that because of the diminished peritoneal capacity the gastric pressure rises rapidly in response to postural change and when combined with swallowing, whether it be air, food, or saliva, regurgitation is liable to occur.

6. *Hiatus Hernia.*—The regurgitation which accompanies sliding hiatus hernia is severe and persistent. Following disruption of the œsophago-gastric angle, reflux is produced whenever the gastric pressure is increased and this happens with any minor bending action. As a consequence regurgitation occurs whether the stomach is full or empty and the lower œsophagus is continuously bathed with gastric contents. Because of this continuous trauma, probably unremittent even during sleep, the œsophagus undergoes inflammatory changes and the symptoms of severe regurgitation dyspepsia are aggravated by the presence of œsophagitis. It is only the persistence of the reflux preventing recovery which causes the symptomatology to differ from the more benign forms of reflux dyspepsia.

Discussion.—Heartburn, flatulence, and postural regurgitation form a triad of symptoms produced by persistent reflux of stomach contents into the œsophagus. This syndrome is widely recognized in association with sliding hiatus hernia, but it is not so well appreciated that identical, though usually less severe and persistent, symptoms can occur in the absence of gross pathology. Lawler and McCreath (1951) investigated 53 patients with postural regurgitation and found 34 hernias amongst them. Where the symptoms are so pronounced that the patients seek medical advice it is probable that similar proportions will pertain, but if less severe degrees of postural regurgitation are investigated then it will doubtless be found that those with hiatus hernia form but a small fraction of the total. After all, the symptoms are not dependent upon the hernia but upon regurgitation.

In this essay no attempt has been made to determine the relative frequency of the various types of postural regurgitation. The list of causes which has been given simply summarizes an experience of a very limited number of cases and is not necessarily complete. The main purpose in presenting them is to show that the clinical forms of regurgitation result from causes which conform with the basic observations which were detailed at the start of the essay. On analysis it is found that one or more of the following factors is always present in any case of clinical regurgitation, and the importance of these has largely been confirmed by experimentation.

a. Change in posture.

b. Gastric distension.

c. Diminished peritoneal capacity. Pregnancy, adiposity, and other large abdominal tumours are associated with reflux dyspepsia. The symptoms usually disappear after parturition, surgical removal of tumours, or successful weight reduction. It is difficult to escape from the conclusion that the diminished peritoneal capacity is the cause, and it is believed that this acts by allowing only slight gastric distension before the intragastric pressure responds excessively to postural or other factors which produce a sharp passive pressure increase.

d. Swallowing.

e. Loss of the normal gastro-œsophageal angle. This occurs classically in hiatus hernia, but it may also play a part with elderly people who develop postural regurgitation in the absence of a hernia. It is possible that hypotonicity of the diaphragm and widening of the hiatal orifice, which occurs in old age, allows undue mobility of the terminal œsophagus and this may alter the œsophago-gastric angle and impair its efficiency.

The symptoms of these various pathological conditions are all the same because the effects of each is to produce regurgitation. However, it has been shown that reflux of stomach contents is a normal and often silent happening during and immediately after meals, whilst postprandial flatulence without discomfort is so common that it is considered to be quite normal. Regurgitation can be symptomless, it may cause flatulence without discomfort or it may produce heartburn. It would appear that heartburn only arises when persistent regurgitation occurs from a stomach that is not freshly distended with food. Bennet and Ryle (1921) were unable to prove that hyperacidity existed at times of heartburn, and it is known that the typical discomfort can occur with achlorhydria (Alvarez, 1948). The free gastric acid cannot therefore be implicated specifically and neither, it is believed, can any other fraction of the gastric secretion. The burning œsophageal pain, which can be experimentally produced, is caused by mucosal irritation and there is nothing specific about the irritant. In the same way, it may well be that heartburn is caused by different irritants such as acid, pepsin, bile, or perhaps even certain products of partial digestion.

Personal idiosyncrasy may also be important, for occasionally one meets a pregnant woman who admits to flatulence and postural regurgitation but not to heartburn. It is relevant to mention here the case of three men who ate hamburgers prepared from a common source. Two developed severe heartburn, but the third, even though he experienced 'acid-eructations', experienced no discomfort. He had never in his life suffered from heartburn and a gastric analysis on this occasion proved normal.

The factor of the greatest importance, apart from the nature of the regurgitant material, is the persistence of regurgitation. It has been noted that during an attack of reflux dyspepsia, flatulence often precedes heartburn by an hour or more, and this suggests that irritation of the œsophagus must be prolonged before discomfort is caused. Heartburn is therefore a sign of persistent regurgitation, and when the discomfort is itself prolonged the symptoms are liable to become progressively more severe. This is seen in cases of sliding hiatus hernia where the persistent reflux eventually causes inflammatory changes and the intense pain of œsophagitis then develops. On the other hand, with occasional attacks of reflux dyspepsia, œsophagitis does not become established as the mucosa has time to recover between the bouts of irritation and the symptoms do not progress beyond those of intermittent heartburn.

Regurgitation of stomach contents may therefore result in little or no discomfort or it may produce very severe and intractable symptoms. Even though the intensity of symptoms varies so widely, these are in no way specific, for they are due to regurgitation and not to the underlying cause. The more persistent the regurgitation the more severe the symptoms, and this simply depends on the effects of prolonged irritation of the œsophageal mucosa.

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BILATERAL WILMS' TUMOUR

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THE first reported case of a renal tumour in a child—by coincidence, a case with bilateral involvement—appeared in the literature in 1814 (Rance), and since that date it has been universally recognized that, although many busy general surgeons may never encounter one, Wilms' tumour represents one of the commonest malignant tumours found in childhood. The majority of cases appear in the first five years of life, but they have been reported in the fœtus (Nicholson, 1931) and in adults up to the age of 75 years (Twinem, 1946). They are highly malignant, show a marked tendency to recur, and have an overall mortality of almost 90 per cent (Scott, 1954).

Most of the reported cases of bilateral Wilms' tumour have been discovered accidentally at autopsy and there is no doubt that many cases, which have been reported as bilateral, actually represent a unilateral primary tumour with secondary involvement of the opposite kidney.

While many cases have probably been overlooked and others may not have been reported, the presence of bilateral Wilms' tumour is still a great rarity and, for that reason, it is felt that this report of a case which was admitted to the Royal Hospital for Sick Children, Glasgow, may prove a useful contribution to the literature on the subject. In addition, an attempt has been made to present a comprehensive review of all the cases which have previously been reported.

Incidence of Bilateral Cases.—In 1897, Walker collected 141 cases of renal tumours in children, including no less than 10 bilateral, but he failed to give any information about them and Eve, in a paper read before the Pathological Society of London in 1882, described 6 collected cases, of which 4 were bilateral.

In 44 cases of Wilms' tumour reported by Weisal, Dockerty, and Priestley (1943), from the Mayo Clinic, there were no examples of bilateral involvement, and according to Campbell (1948) none were found by Dean in 100 cases seen at the Memorial Hospital, New York. In 1951 the British Association

of Urological Surgeons circulated a *pro forma* to every one of their members requesting information on tumours of the kidney in adults and children and, out of 189 cases of Wilms' tumour collected, only 1 was bilateral (Riches, Griffiths, and Thackray, 1951).

In a recent extensive review of the literature, carried out by the writer during the preparation of a thesis, abstracted details of 906 cases of Wilms' tumour revealed the fact that both kidneys were involved in 33 cases (3·6 per cent).

Clinical Features of Wilms' Tumour.—The first symptom is generally a swelling, partly or wholly filling one side of the abdomen, which is frequently discovered accidentally by the child's mother. Unlike tumours of the kidney in adults, it is rare to have any symptoms referable to the renal tract. Hæmaturia occurs very infrequently, is indicative of spread into the renal pelvis and carries with it an extremely bad prognosis. The reported incidence of hæmaturia has varied from 3 per cent (Dean, 1939) to 21 per cent (Scott, 1954).

Radiological Findings.—Intravenous pyelography may reveal mechanical distortion of the renal pelvis, obstruction of the ureter with hydronephrosis, or elongation of the calices, but commonly shows a functionless kidney on the affected side, with displacement of the bowel shadow downwards and medially by a large ' soft-tissue ' opacity (Scott, 1954). If difficulty is experienced in finding a suitable vein in these infants, the dye may be injected subcutaneously, using hyalase to hasten its absorption. Retrograde pyelography is frequently employed in the American clinics but, in cases where a Wilms' tumour is suspected, it is looked on with disfavour in this clinic, owing to the additional handling of the patient which this investigation entails.

Treatment.—Surgery, used in combination with radiotherapy, is the treatment of choice in most clinics at the present day. The exact role of radiotherapy has not yet been finally determined, but it is now more or less universally agreed that a course of post-operative therapy is always indicated. Most of these tumours are radio-sensitive and diminish considerably in size following a course of deep X-ray therapy. For this reason it is now frequently employed in a pre-operative role with a view to ' shrinking ' large and apparently inoperable tumours, thereby facilitating their exposure at a later date. The treatment of bilateral cases poses an even more difficult problem, although Rusche (1951) reported a case still alive and well six months later, following nephrectomy, combined with radiotherapy to the opposite kidney, and Gross and Neuhauser (1950) reported a case treated by right nephrectomy, with pre- and post-operative radiotherapy, followed by intensive radiotherapy to the opposite kidney. The child was alive and well twelve years later.

CASE REPORT

J. C., female, aged 11 months.

HISTORY.—This girl was a face presentation at birth but no instruments were used in delivery. She was breast fed for three months, during which time she had a short attack of whooping-cough. She had cut two teeth at five months and by nine months was able to stand upright without support. Three months before admission her mother noticed a swelling in the left side of her abdomen and since then she had lost her appetite and become obstinately constipated. Latterly, she had vomited up every feed. There was no history of any urinary symptoms.

CLINICAL EXAMINATION.—Height 69 cm. She was a fat child with a tendency to flabbiness. There was no glandular enlargement, the mucous membranes were well coloured, and no abnormality was detected in her eyes, ears, nose, or throat. The respiratory, cardiovascular, and central nervous systems were all normal. The tongue was clean and moist. Both Mantoux and Von Pirquet skin-tests were negative.

ABDOMINAL EXAMINATION.—A large, non-tender swelling extended from the left costal margin down to a line, 1½ in. below and to the left of the umbilicus, completely filling the left hypochondrium and left loin. The surface of the mass was nodular and its upper border could not be determined. It was freely mobile and moved with changes in the child's position.

SPECIAL EXAMINATIONS.—

Urinalysis.—The urine was acid and contained a trace of albumin. Renal cylindrosis was present.

Hæmatology.—Hæmoglobin 60 per cent; red-cell count 5,230,000 per c.mm.; white-cell count 23,000 per c.mm.; colour index 0·72. The blood-film revealed slight anisocytosis, and no nucleated red cells were seen. The eosinophil count was 1·2 per cent.

Radiological Picture.—A straight radiograph of the abdomen revealed a large soft-tissue shadow obliterating the whole of the left side of the abdomen and displacing the bowel to the right.

TREATMENT.—The swelling was explored through a left paramedian incision and was found to be a large, and almost inoperable, tumour of the left kidney which was adherent anteriorly to the splenic flexure of the colon. A nephrectomy was performed but the child's condition deteriorated very rapidly during the operation. She never recovered consciousness and died ten hours later.

AUTOPSY FINDINGS.—

Head.—The brain, venous sinuses, middle ears, and cranial bones were all normal.

Thorax.—No gross lesion was found in the heart or pericardial sac. Numerous small hæmorrhagic infarctions were scattered throughout both lungs.

Abdomen.—No gross lesion was found in peritoneum, bowel, liver, or spleen. The right kidney, which was slightly larger than normal, showed numerous pale areas scattered throughout its substance. There was no gross evidence of tumour in any of the renal vessels and none of the local lymphatics appeared to be grossly involved.

HISTOLOGY.—The left kidney, which had been removed at operation, revealed the typical picture of an embryoma and this picture was identically reproduced in each of the scattered pale areas which had been noted on naked-eye examination of the opposite kidney. There was no evidence of tumour cells in the perirenal lymphatics or blood-vessels and the infarcted areas of the lungs were also free from metastatic involvement.

Table I.—CLASSIFICATION OF BILATERAL WILMS' TUMOUR

Group I	Bilateral tumours found primarily at autopsy
Group II	Bilateral tumours—both palpable on admission
Group III	Unilateral tumour palpable on admission. Opposite kidney found to be involved on clinical examination at a later date
Group IV	Unilateral tumour palpable on admission. Opposite kidney found to be involved at autopsy
Group V	Cases reported in the literature, in which neither history nor clinical findings were recorded.

REVIEW OF THE LITERATURE

In order to facilitate discussion and, at the same time prevent constant repetition, an attempt has been made to form an arbitrary classification of the

reported cases—based on the method by which they were diagnosed (*Table I*).

Details of the authors, together with the age and sex of the patients (where available), have been grouped together in *Table II*.

Wilms' tumour, in contradistinction to sympathicoblastoma, rarely spreads across the midline, and Rusche (1951) reported a case (not *Case* 26) in which there was a Wilms' tumour of one kidney with secondary invasion of the perirenal tissues on the

Table II.—BILATERAL WILMS' TUMOUR
(Summary of 33 Recorded Cases)

CASE NO.	AUTHOR	SEX	AGE	GROUP (*See Table I*)	CASE NO.	AUTHOR	SEX	AGE	GROUP (*See Table I*)
1	Rance (1814)	F.	17 mth.	III	16	Kretschmer and Hibbs (1931)	M.	5 mth.	IV
2	Gairdner (1828)	F.	3 yr.	I	17	Kretschmer and Hibbs (1931)	M.	1 yr.	III
3	Eberth (1872)	F.	17 mth.	I	18	Ueda (1935)	Not stated	8 mth.	IV
4	Hansen (1873)	Not stated	10 mth.	V	19	Ladd (1938)	F.	6½ yr.	II
5	Cohnheim (1875)	Not stated	16 mth.	I	20	Stern and Newns (1938)	M.	2 yr.	I
6	Weigert (1876)	Not stated	Fœtus	V	21	Kerr (1939)	M.	3½ yr.	I
7	Landsberger (1877)	Not stated	7 mth.	I	22	Campbell (1948)	M.	24 dy.	I
8	Abercrombie (1879)	M.	3 yr.	IV	23	Campbell (1948)	M.	18 mth.	II
9	Abercrombie (1879)	F.	2 yr.	IV	24	Harrison (1948)	M.	1 yr.	II
10	Abercrombie (1879)	F.	4 yr.	IV	25	Barr and Schulte (1950)	M.	4½ yr.	II
11	Abercrombie (1880)	M.	18 mth.	I	26	Rusche (1951)	Not stated	Not stated	II
12	Eve (1882)	Not stated	Not stated	V	27	Sheach (1953)	F.	1 yr.	II
13	Merkel (1898)	M.	6 mth.	V	28	Huguenin and Gerard-Marchant (1953)	Not stated	Not stated	V
14	Strong (1903)	M.	4 yr.	III	29–32	Gross (1953)	Not stated	Not stated	V
15	Loughnane (1914)	F.	18 mth.	II	33	Scott (1954)	F.	11 mth.	IV

From this table it can be seen that, as with Wilms' tumour in general, both sexes show an equal incidence of bilateral involvement and the ages range from twenty-four days to six years.

DISCUSSION

The most controversial and, indeed, the most interesting, point concerns the question, " Are both tumours separate primary growths or is one kidney primarily involved, with metastatic spread to its opposite number? "

In support of the latter theory, the writer has been impressed by the large number of cases occurring in patients who died of advanced malignant cachexia, where no attempt had been made to deal with the primary growth and in whom the bilateral involvement was only discovered at autopsy. Since nephrectomy, either alone or used in conjunction with radiotherapy, has become the accepted form of treatment, the proportion of bilateral cases has dropped markedly. Indeed, out of a total of 234 cases of Wilms' tumour reported between 1814 and 1903, no less than 14 (6 per cent) were found to be bilateral, whereas in 672 cases reported between 1903 and 1953—in which details of the side involved were recorded—only 19 (2·8 per cent) were bilateral. These figures suggest to the writer that, if the tumour is left alone and allowed to progress to a fatal termination, it may in time metastasize to the opposite side.

This secondary spread, if present, is almost certainly not due to direct invasion of the opposite kidney, as it is an accepted fact (Gross, 1953) that opposite side but with no involvement of the actual kidney substance.

The 9 cases in Groups III and IV all tend to suggest secondary involvement of the other kidney, particularly those cases in which a tumour appeared on the opposite side some time after the first tumour had been detected (Group III). In Rance's case a swelling was first noted in the left loin, and six months later a second swelling appeared in the right loin. In Strong's patient the second tumour made its appearance three weeks after a nephrectomy had been performed on the opposite side. Kretschmer and Hibbs' (1931) patient (*Case* 17) had a right nephrectomy performed for Wilms' tumour. The child developed post-operative anuria and decapsulation of the left kidney was performed, during which it was noted that " the kidney was enlarged and pale, but free from tumour ". Five weeks later, a mass appeared in the left loin and laparotomy revealed a typical Wilms' tumour. The child died shortly afterwards and, in addition to bilateral renal involvement, metastases were found in the liver and lung. This case, at least, appears to be a genuine example of metastatic involvement of the remaining kidney.

The case described by Ritter and Scott (1949) has not been included in the present series, but it does seem worthy of mention, although the interval of time elapsing between the discovery of the separate tumours was very much greater. In this case, the second kidney became involved ten years after an apparently successful nephrectomy and, as there were no other metastases elsewhere in the body, this

second tumour was considered by the authors to be a second primary growth.

On the evidence of some of the reported cases, it would seem that at least a few of them were examples of bilateral primary involvement, particularly those cases falling into Group II. Of interest in this Group is the case described by Barr and Schulte (1950), where the child had been in hospital six months previously (for another complaint) and no mass was palpated in his abdomen. On the second admission masses were palpable in both flanks, and the diagnosis was confirmed at autopsy.

In the case which is reported from this hospital (*Case* 33), although the second kidney was involved in several discrete areas, suggesting metastatic spread, there was no macroscopical or histological evidence of tumour cells in the surrounding lymphatics or blood-vessels and, after all, if primary Wilms' tumours can arise spontaneously in opposite kidneys in identical monovular twin boys (Gaulin, 1951), why shouldn't they arise spontaneously in a normal monovular child?

SUMMARY

A case of bilateral Wilms' tumour is presented. The clinical and radiological features of Wilms' tumour, together with a summary of the treatment, are briefly recorded.

The literature on bilateral Wilms' tumour is extensively reviewed and it is suggested that the majority of reported cases represent metastatic spread to the opposite kidney, although a few, at least, do appear to represent bilateral primary growths.

I wish to thank the Medical Superintendent of the Royal Hospital for Sick Children, Glasgow, for permitting access to the hospital records and would like to express my gratitude to Mr. Matthew White for invaluable criticism and advice in the preparation of this paper. Finally, a word of thanks to Dr. Beck, of the Research Department, Royal Beatson Memorial Hospital, Glasgow, for his translations of the German papers, without which this paper would have lost much of its value.

Addendum.—Since this paper was submitted for publication, the writer has encountered a further example of bilateral involvement in which the right kidney was primarily involved and, at autopsy, tumour tissue was traced along the right renal vein, the inferior vena cava, and the left renal vein right into the substances of the left kidney.

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SACROCOCCYGEAL CHORDOMA

BY JOHN A. SHEPHERD, LIVERPOOL

"IT has been amply demonstrated that until a new and revolutionary method of operating in sacrococcygeal chordoma is devised and made practical the patient who develops this long drawn out disease has little to look forward to in life."—Coley in *Neoplasms of Bone.*

LITTMAN (1953) estimates that 160 examples of sacrococcygeal chordoma have been reported. These comprise about 50 per cent of the tumours of this type in the notochordal situations—about 37 per cent are cranial in position, and the remainder lie along the vertebral column.

The accepted embryological facts need not be repeated in detail. In the last hundred years Luschka, Virchow, and Muller respectively discovered, described, and elucidated chordomatous tumours. Ribbert, in 1895, by puncturing the intervertebral disks of rabbits produced chordoma-like growths. Hennig in 1900 gave the first description of a sacrococcygeal tumour in a seven-months fœtus. (Reference may be made for details of this early history to the following reviews: Stewart (1922), Cappell (1928), Bruce and Mekie (1937), Harvey and Dawson (1941), Birrel (1952), and Littman (1953).)

In presenting a further example of sacral chordoma it is proposed to discuss the origin, frequency, diagnosis, and pathology only in so far as these influence treatment and prognosis.

In the early embryo the notochord becomes a solid column of cells stretching from head to tail. The spinal column forms around the notochord and the latter structure disintegrates. Notochordal tissues may persist as the nucleus pulposus or in scattered nodular remnants in certain positions in some 2 per cent of humans. Usually these remnants remain quiescent—rarely they grow as tumours. Ribbert's experiments have favoured the idea that trauma may release notochordal cells and when these cells escape they multiply. Sacrococcygeal chordoma might be due to trauma, but injury to the tail is so common that its true relation to tumour formation is uncertain. Alternatively chordoma may arise from abnormally situated cells—projecting, for example, beyond the tip of the coccyx, or lying unsupported and exteriorized because of some bony defect of the sacrum. Release from the tense barrier of bone is thought to favour proliferation.

These are theories and, by the time a sacrococcygeal chordoma presents, the lower third of the sacrum is usually grossly involved and it is quite impossible to trace the exact origin. From recorded cases it can but be suggested that these tumours arise initially from the points of fusion of the coccygeal or sacral segments. Primary sacrococcygeal tumours have not been seen separate from bone, although in the neck isolated chordomata have been described without direct attachment to bone.

Microscopically chordoma resembles primitive notochord very closely. A typical tumour is often well encapsulated and divided into lobules by fibrous trabeculæ. The cells at the periphery of the lobule are closely packed and epithelial in type. Towards the centre of the lobule vacuolation is marked and the characteristic 'bubble' cells and 'signet-ring' forms appear with their high mucin content. In the centre some of the cells disintegrate and are replaced by a mucinous syncytium.

The lobulated tumour is translucent and gelatinous. In some areas there may be necrosis or hæmorrhage. The neighbouring bone is at first expanded and then it is destroyed. The radiographs show translucencies, then complete defects. Occasionally bone spiculation is seen around the tumour, or there is a shell of new calcification.

In the early stages the tumour presents as a smooth projection anteriorly or posteriorly on the sacrum. Extension after bone destruction may involve the sacral nerves, the surrounding soft tissues, and even the rectum.

FIG. 643.—Irregular defect to left side of 3, 4 sacral segments. Patchy sclerosis on mid-portion.

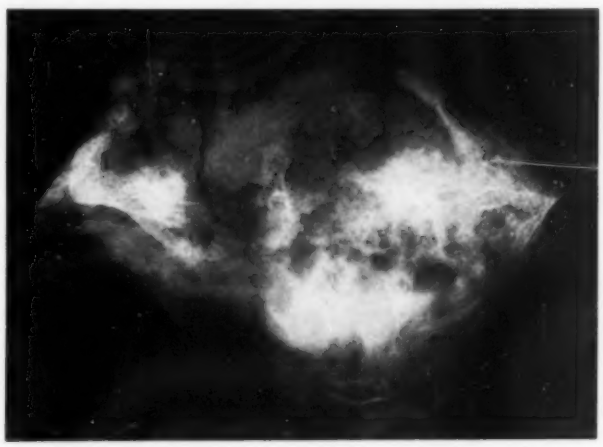

FIG. 644.—Excised bone showing the gross bone destruction to one side and sclerosis centrally.

The chief symptom, and an early symptom, is pain. This may be present for years before the tumour is clinically obvious. Local anæsthetic effects, bladder dysfunction, and rectal disturbance are symptoms of advanced disease. For months or years the sacral discomfort is attributed to one or other of the common orthopædic or gynæcological causes of sacral pain. The diagnosis depends on the palpation of the swelling or the recognition radiologically of bone destruction.

The following case shows most of the characteristics of the disease in its history and course.

Case.—Mrs. S., aged 72, was first seen in February, 1952, complaining of persistent discomfort in the rectum of eighteen months duration. For many months her urine had been foul-smelling and she had suffered from frequency. Her bowels were regular but she had the sensation of failing to empty the rectum completely. A continuous nagging pain in the sacral region was aggravated by sitting. One year before she had been seen by a gynæcologist, who diagnosed and removed a calcified fibroid. He did not promise relief of pain and his pessimism was confirmed.

ON EXAMINATION.—There was tenderness over the lower three segments of the sacrum posteriorly. Per rectum there was felt a symmetrical central protrusion from the concavity of the sacrum, indenting but not invading the bowel. The tumour was fixed, firm, and rather elastic. It was smooth, and about the size and shape of the blunt half of a hen's egg. A diagnosis of chordoma was made on account of the position of the tumour, the character of the pain, and the long history. Arrangements were made to admit her to hospital for radiological investigations and sigmoidoscopy.

A few days later she was rushed in because of severe and sudden hæmaturia. An intravenous pyelogram was done and showed a filling defect in the right kidney and

bone changes were shown in the lower half of the sacrum (*Fig.* 643). The diagnosis was hastily changed to hypernephroma with metastasis in the sacrum. (Birrel, 1952, describes a similar error in diagnosis.) It was decided to confirm this diagnosis by exploring the sacral mass—now quite an obvious swelling posteriorly.

AT OPERATION (Feb. 27, 1952).—A curved incision was made vertically over the sacrum and coccyx. The rectum was readily pushed away from the sacrum and the lateral muscular attachments to the lower segments of the sacrum were divided close to the bone. A smooth lobulated black glistening tumour was found replacing the major mass of the three lower sacral segments. The appearance suggested hypernephroma. (In fact it was typical of chordoma, but this was the first personally encountered.) In the belief that a solitary metastasis from a kidney tumour had been exposed and that a nephrectomy might be achieved later, the affected segments of sacrum were excised in a block. As far as could be judged a section was made through healthy bone well above the tumour level. The third sacral nerves were seen and one was thought to be preserved intact. The wound was closed and the cavity packed with 'Vaseline' gauze and drained from below. Immediate post-operative healing was very satisfactory. The tumour was reported as a chordoma (*Figs.* 644, 645).

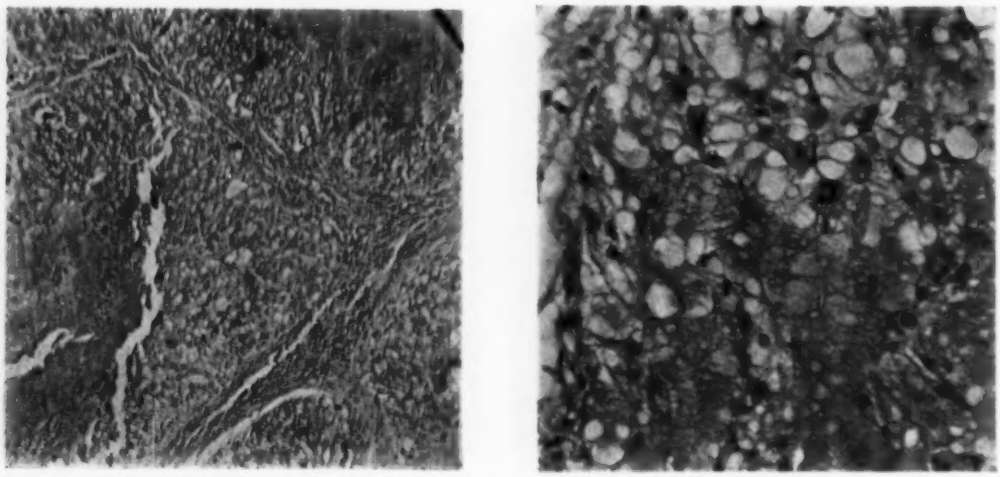

FIG. 645.—Low-power and high-power photomicrographs of tumour.

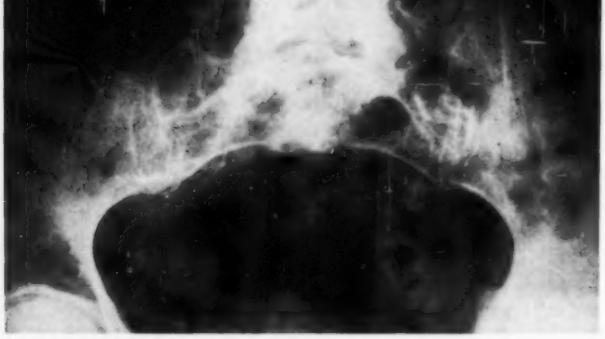

FIG. 646.—Extent of bone resection.

SUBSEQUENT PROGRESS.—On March 15 an urgent operation had to be done for a strangulated femoral hernia. This caused little inconvenience to a placid and stout-hearted lady. On March 25 a further intravenous pyelogram showed that both kidneys were now normal in appearance but that there was very poor evacuation of the bladder. On April 3 she was discharged from hospital requiring daily rectal washouts but with adequate urinary control.

She carried on free from pain and remarkably active until April, 1953, when a persistent throbbing pain returned at the site of the wound and a swelling developed externally. She was readmitted and found to have a large tender diffuse cystic swelling over the lower sacral area. The radiograph showed no more bone loss than appeared in a plate taken after her first operation. Exploration was planned in the hope of relieving her severe pain by, at least, decompressing the tumour.

SECOND OPERATION (May 20, 1953).—A vertical incision was made over the mass and a smooth-walled cystic space was entered. This had the appearance of a large adventitious bursa and beneath it lay a smooth lobulated chordomatous mass. With difficulty the tumour was dissected from the surrounding tissues. It was firmly attached to the lower edge of the sacral remnant and it was impossible to achieve a clean bone section at this level because of irregular spiculation and an indeterminate tumour margin. The extent of the bone removal is shown (*Fig.* 646).

FURTHER PROGRESS.—Healing was again rapid and relief of pain dramatic. The urinary symptoms were much aggravated and an indwelling catheter was required permanently. On June 23, 1953, she was discharged. On Feb. 28, 1955, she was found to be very fit, with unimpaired renal function and no sign of a recurrent tumour. There was no herniation of the rectum.

DISCUSSION

Untreated a sacrococcygeal chordoma grows inexorably. To judge by all published reports there is inevitable recurrence after local excision. The recurrent tumour is usually identical histologically with its predecessor. Blatant malignancy—that is, with metastases—has been observed in less than 10 per cent of cases. The malignant chordoma is more solid and shows less mucoid degeneration than the simple growth; if metastases occur they are mainly in the liver or in lymph-nodes. Stewart (1922) describes the slow appearance of metastases in a patient on whom Lord Moynihan operated in 1912.

The picture described in the present case mirrors general experience, and because the surgeon sees so few examples in a lifetime he is only vaguely aware of the fruitless quest for more successful treatment. Littman (1953) states that there is no proved record of freedom from recurrence after excision. Birrel (1952), however, records one patient with a small coccygeal tumour which was excised where there was no recurrence after nine years' observation. It is true that operative treatment has given considerable prolongation of life and even some deferment of complete disability, but a survival satisfactory in terms of years has often been obtained at the cost of a miserable invalidism.

The problem of treatment is quite simply stated. Sacral chordoma is not usually detected until it has spread widely in the bone. A radical excision beyond the apparent spread of the tumour is usually limited by an attempt to preserve at least one of the third pair of sacral nerves—so to preserve the bladder function. If bladder function is already impaired there is the orthopædic consideration of leaving intact the keystone of the pelvic ring. Finally, a high excision leads to disturbance of bowel control and a tendency to herniation of the rectum through the incision.

The reason for the inevitable local recurrence is uncertain. Some recurrences may follow a failure to remove in one block all the original tumour. In theory spillage of cells may lead to implantation of a new growth. It is, however, difficult to believe that a few early tumours have not been excised widely surrounded by a shell of normal tissue—yet *all* cases seem to recur eventually. Perhaps after the first excision a new nodule of chordomatous tissue—hitherto quiescent—becomes activated and starts multiplying at a higher level in the sacrum. Multiple sources of tumour formation may lie in a chain right through the sacrum and even to the lumbar vertebræ. The trauma of operation may set off new growth.

The question must be asked as to whether or not preoccupation with anatomical and physiological considerations may result in a failure to treat this recurrent and often lethal condition as thoroughly as might be done. Gentil and Coley (1948) have written "radical surgery naturally involves difficulty with regard to bladder and rectal control. It has occurred to us that these difficulties might be overcome by permanent colostomy and uretero-enterostomy"—but they dismiss the idea as objectionable. The Mixters (1940) have said: "we do not know whether it is feasible to resect the upper two segments of the sacrum." McCarty, Waugh, Mayo, and Coventry (1952) have advocated a more careful and more extensive local excision but stop short of drastic measures such as ureteric implants. Littman (1953) has remained conservative but has stressed the need for the co-operation of the neurosurgeon, the orthopædic surgeon, and the general surgeon in the management of these difficult problems. Radiotherapy has been used frequently, but the effect is uncertain except in relieving pain in a few cases.

That most of the sacrum can be resected without causing grave functional disability is shown by the present case. In treating giant-cell tumour of the sacrum Bowers (1948) reports resection of all but the first segment and control of excretory function by "penile clamp and constipating diet". In a similar case Hays (1953) left only a narrow bridge of the first sacral segment and the patient could walk with a leg brace.

In theory better results might be hoped for by doing the primary excision at the highest possible level. In cases where there is already disturbance of bladder and rectal function a high resection is readily justified and, as in the present case, rectal and bladder control can be achieved by simple means. The most difficult group of patients remains—young patients in whom there is no bladder and rectal dysfunction. Here there might appear to be a case for a high resection leaving only part of the first arch, for transplantation of the ureters and colostomy. In the surgery of other malignant conditions—using the term malignant widely—'radical' methods are advocated without flinching, and may involve the destruction of normal functions and often the production of gross deformity. It would require great courage to advise such radical treatment for sacral chordoma unless there could be a reasonable certainty of freedom from recurrence by the procedure. Until the source of origin of recurrent chordoma is elucidated such crippling methods are unjustifiable. The experience of the present case supports the view that repeated excision is well worth while and that high resection is possible without causing crippling deformity or necessitating diversion of urine and fæces.

SUMMARY

Sacrococcygeal chordoma is a rare condition. Despite its inevitable recurrence after local excision there is no justification to advocate more radical operations than excision of the affected segments of sacrum. A case is described where repeated local resection has maintained reasonable comfort despite rectal and vesical paralysis. Until the source of recurrence is elucidated no advance in treatment can be expected.

My thanks are due to Dr. F. Whitwell, of the Department of Pathology, Broadgreen Hospital, for his reports on the slides; and to Mr. Wilfred Lee, of the Central Medical Photographic Department of the University of Liverpool, who prepared the prints and photomicrographs.

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CAROTICO-CAVERNOUS FISTULA WITHOUT PULSATING EXOPHTHALMOS

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Despite its rarity, the carotico-cavernous fistula has received frequent mention in the literature. Its unique qualities, the ease of making the diagnosis when one is aware of the syndrome, and the satisfaction derived from doing so, as well as the not infrequent gratifying results of treatment, perhaps explain this publicity. Although Dandy (1937) thought it unlikely that there was much to be added to the clinical picture, the subject has not been entirely exhausted and, when in a case one of the cardinal features is absent, mention should be made of this exception.

Fig. 647.—Photograph of patient showing left ptosis and mild œdema of upper lid.

We thus propose to record a case of traumatic carotico-cavernous fistula where pulsating proptosis was not detected, and to discuss the causes of this unusual event.

Nomenclature.—Pulsating exophthalmos is one of the striking features manifested by a carotico-cavernous fistula. It may, on rare occasions, however, accompany other vascular lesions, when the clinical picture can be indistinguishable from the spontaneous type of fistula (ophthalmic artery aneurysm—Heimburger, Oberhill, McGarry, and Bucy, 1949; Sverdlick and Veppo, 1951: orbital angioma—Delord and Viallefont, 1932). Furthermore, pulsation may not accompany a fistula, and it would thus be fallacious to accept the suggestion of Keller (1898) and Dorrance and Loudenslager (1934) that 'pulsating exophthalmos' and 'carotico-cavernous fistula' be considered as synonymous terms.

Because of differences in nomenclature, some confusion has occurred in the literature and we would submit that as cerebral angiography is now available to verify the diagnosis, the term 'pulsating exophthalmos' should be retained as a descriptive epithet and that it should not be applied to a clinico-pathological entity.

Pulsating Proptosis in Carotico-cavernous Fistula.—This is due to a reversal of blood-flow in the ophthalmic veins that normally feed the cavernous sinus. An arterial pulsation is thus transmitted to the eyeball. The degree varies considerably and in some cases it may only be detected by palpation of the globe. Severe chemosis and orbital œdema may, however, mask it (Guillaume, Dollfus, and Rogé, 1952) and it may be delayed (Riordan and Nees, 1935; Ehlers, 1929).

Fig. 648.—Photograph of patient showing proptosis and chemosis.

On occasions authors have avoided the diagnosis of carotico-cavernous fistula in the absence of pulsating exophthalmos (Brock, 1929), but that such cases do occur is substantiated by the following case report.

CASE REPORT

Female, aged 71. Fracture of left middle fossa producing carotico-cavernous fistula on that side. Proptosis and orbital œdema not severe and no ocular pulsation. Angiogram demonstrated fistula with posterior drainage only. Spontaneous improvement, but fistula still patent twelve months after injury and ocular signs unchanged.

Mrs. E. G. (Hospital No. 152802), a housewife aged 71, was admitted to Hammersmith Hospital on Sept. 18, 1953, under the care of Mr. R. H. Franklin.

She had been knocked down by a bus and on admission, half an hour after the accident, she was unconscious and bleeding from both nostrils and from the left auditory

meatus. The left pupil was dilated and both pupils were fixed to light. The tendon reflexes were brisk and equal and there were bilateral extensor plantar responses. Pulse, respirations, and blood-pressure were normal. There was a fracture at the middle of the shaft of the right clavicle and radiographs showed a linear fracture of the left squamous temporal bone which was extending into the middle fossa.

PROGRESS.—Twenty-four hours after admission, she was still unconscious, but the pupils were now normal.

FIG. 640.—Cerebral angiogram, left lateral view. Dye is filling the left internal carotid artery only as far as the cavernous sinus, which is outlined.

Over the next five days she gradually regained consciousness and it was then noted that there was a complete left ophthalmoplegia and that she was blind in that eye. Hypalgesia was found in the distribution of the left ophthalmic division of the trigeminal nerve. The fundus oculi was normal, but gradually œdema of the left eyelids appeared and chemosis developed. This was of only mild degree and the proptosis was likewise not marked (*Figs.* 647, 648). No pulsation of the eyeball was detected at any time either by inspection or by palpation. A loud bruit, synchronous with the pulse, could be heard all over the head, but it was loudest in the left frontal region and was obliterated by compression of the left internal carotid artery.

A left cerebral angiogram revealed that the dye in the internal carotid artery did not extend beyond the sellar region and that the cavernous sinus was outlined (*Fig.* 649). A later exposure (4 seconds after the injection) showed the left internal jugular vein (*Fig.* 650), indicating that the dye was escaping posteriorly. No channels in the orbit were visible and no intracranial filling of arteries or veins had taken place.

Apart from the ocular signs and a persistent right extensor plantar response, the nervous system was normal. She was, however, confused and irrational and she did not complain of head noises. During the following two weeks the proptosis decreased, the orbital œdema subsided, and the bruit changed in character and became more high-pitched and less loud. On discharge, six weeks after admission, the ophthalmoplegia, the blindness, the bruit, and the extensor plantar were still present but the proptosis had now almost disappeared. Good union of the fractured clavicle had occurred.

The patient was seen twelve months after discharge. Her mental faculties were normal and she now admitted that occasionally when in bed she noticed " pulsations in the head ". The physical findings were unchanged.

Comment.—Pulsation of the eye was at all times absent and the proptosis was never marked. The angiograms showed that blood from the fistula was escaping mainly through posterior channels. It is possible that this accounts for the unusual findings and that thrombosis, anteriorly in the cavernous sinus, was taking place. This process perhaps also explains the spontaneous improvement which occurred. Cerebral

FIG. 650.—Cerebral angiogram, left lateral view taken 4 seconds after that reproduced in *Fig.* 640. Dye is still visible in the internal carotid artery, but in addition it is now seen in the adjacent internal jugular vein.

angiography has been known to precipitate it (Parsons, Guller, Wolff, and Dunbar, 1954; Potter 1954), but this procedure played no apparent role in our case. In view of the diminution of proptosis and the change in the quality of the bruit (Keegan, 1933), we at first believed that spontaneous closure of the fistula was taking place. In view of her age, the severe ocular damage and the initial recovery, no active therapy was employed and so far it seems that this decision has been justified. The extensor plantar response on the right was due either to local cerebral trauma or to diminished blood-supply to the left cerebral hemisphere.

DISCUSSION

Sattler (1920, p. 37) noted the absence of pulsating proptosis in only 5 per cent of 246 cases of carotico-cavernous fistula and his 13 cited case reports have been verified. An additional 4 cases (Case No. 32, 50, 52 and 66) collected by De Schweinitz and Holloway (1908, p. 20) have not been accepted because of inadequate evidence and 2 cases (Case No. 44 and 83) of Keller (1898, p. 135) are likewise excluded. Using strict criteria, the incidence has been estimated in 170 cases appearing in the literature since 1920. In only 138 of the reports was there a definite statement made concerning pulsation and, of these, in 22 (15 per cent) it was said to be absent. Palpation of the eye may not have been employed in all, so the frequency is probably less than this analysis suggests.

Thus, if our case is included, there is a total of 37 instances where a carotico-cavernous fistula did not produce pulsating proptosis. Consideration of the whole group reveals the reason for this paradoxical behaviour.

The Absence of Pulsation.—No detailed attempt has been made in the past to explain this and McNair (1940), despite the title of his article, does not discuss it.

The presence or absence of pulsating proptosis seems to depend ultimately upon the arrangement and function of the channels feeding and draining the cavernous sinus. If the main drainage of the carotico-cavernous fistula is through the ophthalmic veins, pulsation of the eye would be expected to be present, but if the blood proceeds posteriorly or takes other routes, pulsation is less likely to occur. Evidence in support of this can be gained from anatomical, pathological, clinical, and angiographic sources.

1. *Anatomical Evidence.*—Edwards (1931) has shown the variations in the intracranial sinuses and venous channels that are found in the normal, and the cases of Dandy and Follis (1941) demonstrate the events that take place when a carotico-cavernous fistula develops in the presence of these anomalies. In their first patient, a left-sided fistula produced signs in the right eye rather than the left because the left superior ophthalmic vein was thrombosed and the petrosal channels as well as the inferior ophthalmic veins were congenitally absent. Thus the only route of escape was for the blood to cross to the opposite sinus and leave by way of the right superior ophthalmic vein. The left eye was protected from arterial blood and so showed no pulsation. There was " no definite pulsation " in their second case and, although blood drained anteriorly into the orbit, some went by way of the posterior channels, thus probably dissipating the arterial pulse. Tamler (1954) also considered this possibility.

The ophthalmic veins have no valves (Delens, 1870) and lie in soft, yielding tissue. Thus dilatation and reversal of blood-flow readily occur, whereas the petrosal sinuses are bounded by rigid structures so that this is less likely to take place (Locke, 1924). Flow to the opposite sinus by way of the connecting channels will depend upon their patency. Constriction of the superior ophthalmic vein, however, may possibly occur at the superior orbital fissure and so modify the blood-flow (Lopez Villoria, 1929).

The pre-morbid relations of the cavernous sinus therefore play a role in determining the direction that the escaping blood takes when a carotico-cavernous fistula is formed.

2. *Pathological Evidence.*—

a. Thrombosis: Thrombosis within the cavernous sinus or its connexions would be expected to influence the clinical picture. In the first case of Dandy and Follis (1941) already cited, thrombosis of the superior ophthalmic vein protected the eye from pulsation. A very similar example was described by Geis (1941); blood had not only extended to the opposite side but was also escaping posteriorly, as was evidenced by a pulsation in the internal jugular vein. Similar cases have been reported by Nuel in 1902 (also cited by Sattler, 1920), Pincus (1907), Tamler (1954) and possibly Morton (1876). Pulsating proptosis was absent in the patient of Neff (1903, Case 2) and thrombosis in the cavernous sinus occluding the ophthalmic veins was found at autopsy. Likewise, Eitzen (1946) thought that the old lamellated clot in the anterior part of the sinus in his patient was probably obliterating the ophthalmic veins and thus preventing the appearance of pulsation and severe proptosis.

Stuelp (1897) describes the opposite state of affairs, for pulsating proptosis was present in his case and, whereas the petrosal sinuses and the posterior portion of the cavernous sinus were thrombosed, the ophthalmic veins and the anterior sinus were widely dilated.

Thrombosis in the cavernous sinus or its connexions will thus alter the clinical picture according to its location. Atherosclerosis being common in the intrasinus part of the internal carotid artery (Hultquist, 1942), this process would be expected to occur more frequently in the elderly patient, as was so in our case and that of Knudtzon (1950), at least. But although pulsating proptosis may be prevented, the orbital œdema characteristic of septic cavernous sinus thrombosis may appear.

b. Size of the fistula: Delore, Aurand, and Roland (1926) considered this of importance in determining the presence of pulsation and they correlated a small hole with its absence. However, Dandy (1937) could find very little evidence in the literature to suggest that this factor and the degree of exophthalmos were related. He had the impression, nevertheless, that they were. Furthermore, there may be more than one fistulous opening, but again information is insufficient.

c. Site of the fistula: Although Mense (1951) has emphasized the importance and Poppen (1951, Fig. 27) has depicted the expected events, no correlation between this factor and proptosis and pulsation has been attempted in the past. It is conceivable, however, that a fistula posteriorly placed might allow thrombosis to take place anteriorly in the cavernous sinus, and vice versa (Tamler, 1954).

d. Destruction of the superior orbital fissure: Lopez Villoria (1929) has reported a very interesting case. In a patient with a traumatic fistula, pulsation and orbital œdema were absent and the proptosis was very slight. This was owing to damage to the sphenoid bone, so that the superior orbital fissure was destroyed and the orbit was thus cut off from the fistula. Trauma had produced the same results as thrombosis or a congenital anomaly. Radiographs showed that this had not happened in our patient.

e. Dilated internal carotid artery: This may obstruct the ophthalmic veins by direct pressure (Nuel, 1902; Tamler, 1954).

3. *Clinical Evidence.*—A study of the 37 cases where ocular pulsation was not detected reveals that the only possible clinical peculiarities are those relating to the proptosis and to the orbital engorgement.

In 33 cases, the proptosis was either moderate or slight; in 4 cases it was very slight (Lopez Villoria, 1929; Mense, 1951; Potter 1954; authors' case). Orbital œdema was either absent or very slight in 8 cases (Kipp, 1888; Johnson, 1896; Karplus, 1900; Berry, 1905; Bettremieux, 1909; Lopez Villoria, 1929; Rubino and Quarti, 1939; authors' case) and a severe degree was found in only a sixth of them.

It thus seems that the usual severe degree of orbital and ocular congestion occurs less frequently in these special cases, again indicating that predominantly anterior drainage is more rare in them. It may, however, accompany thrombosis in the cavernous sinus which is itself preventing pulsation.

4. *Angiographic Evidence.*—Since the introduction of cerebral angiography it has been possible not only to confirm the diagnosis during life and plan therapy, but also to study the drainage of the carotico-cavernous fistula. Wolff and Schmid (1939) have indicated the six possible exit routes from the cavernous sinus and our case belongs to their third group, in which drainage is posterior.

In 25 cases from the literature and in our case it has been possible to correlate the angiographic appearances with the presence or absence of pulsating proptosis. Angiographic examination was rarely complete, so conclusions can only be tentative. Eighteen had pulsation and in 15 of these drainage was by the anterior route exclusively; in 3 (List and Hodges, 1946, Case 15; Ruggiero and Castellano, 1952, Case 10; Mense, 1951), other routes as well as the anterior were in use. In 7 cases pulsation was absent and in 3 (Wolff and Schmid, 1939, Case 3; Potter, 1954; authors' case), no dye travelled anteriorly. In Case 65 of Engeset (1944) there was neither proptosis nor pulsation and blood drained posteriorly so that lower cranial-nerve palsies were produced by the engorged venous channels. The only case with an outflow via the vein of Labbé alone is that of Dueker and Sanchez-Perez (1947, Case 1). Some anterior drainage was present in the rest of the seven cases (Mense, 1951, Cases 1 and 2; Parsons and others, 1954), but other routes were also in use; ocular pulsation had, however, been inadequately sought after in these cases.

The ability of the blood to reach the cerebral vascular system, although some measure of the size and multiplicity of the fistula, could not be correlated with the presence or absence of pulsation.

The angiographic evidence, being dynamic, is the most valuable of all and it further supports the supposition that the absence of pulsating proptosis indicates a lack or deficiency of flow through the ophthalmic veins and that other channels are being used by the escaping arterial blood.

Treatment.—Of the 37 cases reviewed, details of treatment were available in 31. Three made spontaneous recoveries (9 per cent) and a further 4 recovered with non-operative measures. Thus 22 per cent needed non-specific remedies. These figures suggest that spontaneous cure, presumably by thrombosis in the cavernous sinus and plugging of the fistula (Knudtzon, 1950) can take place more readily in this special type of case, because Sattler (1920) found only 5·6 per cent of spontaneous recoveries in his series of 322 cases and the majority of these, and all of the subsequent cases (Di Luca, 1949), manifested pulsating proptosis.

Although non-intervention may be more likely to be successful in these particular patients, on the whole treatment should be the same as for the more usual type and only in special circumstances, as in our case, should advantage be taken of the process of spontaneous recovery. However, a preliminary period of inactivity (Potter, 1954) may be advisable if circumstances allow. The role of hypotensive agents is yet to be evaluated.

CONCLUSIONS

1. The term 'pulsating exophthalmos' cannot be used synonymously with 'carotico-cavernous fistula'.

2. Pulsating proptosis is absent in 10 to 15 per cent of cases of carotico-cavernous fistula.

3. Its absence is due to defective or absent drainage through the ipsilateral ophthalmic veins.

4. Anatomical, pathological, clinical, and angiographic evidence supports this conclusion.

5. Spontaneous cure may occur more readily in these cases, but treatment on the whole should be along orthodox lines.

SUMMARY

A case of traumatic carotico-cavernous fistula without pulsating proptosis has been described and literature concerning this unusual event reviewed.

Non-pulsation is due to an absence or a paucity of drainage from the cavernous sinus through the ophthalmic veins. This may be caused by anomalies or thrombosis of the sinus or its channels, and the size and site of the fistula play a role. Traumatic obliteration of the superior orbital fissure is a rare factor. Clinical evidence, and that derived from angiography in particular, substantiates this supposition.

Spontaneous recovery occurs more readily, but treatment should be the same as with the more usual type of case.

We are grateful to Mr. R. H. Franklin for allowing us to publish this case.

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A LATERAL APPROACH TO THE FRONTAL AIR-SINUS

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MANY and varied surgical approaches to the frontal air-sinus have been designed, all with their own merits and disadvantages. The object of the present communication is to describe and illustrate a lateral surgical approach in the successful removal of a large ivory osteoma of the frontal air-sinus that had eroded the orbit to cause cellulitis and proptosis.

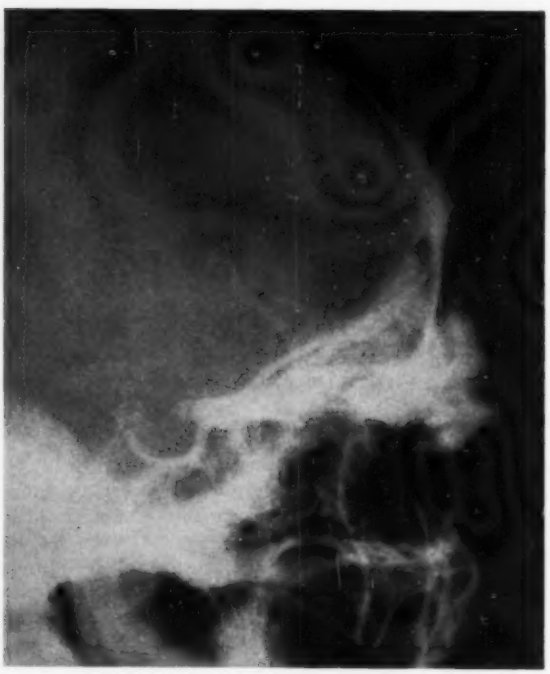

FIG. 651.—The ivory osteoma of the frontal air-sinus is clearly seen.

To be satisfactory, a surgical approach must not only give adequate access to the diseased tissues, but must also allow the surgeon to inspect and protect from injury important structures that lie adjacent. The approach to the frontal air-sinus about to be described, we believe, fulfils these conditions and, moreover, produces minimal residual deformity.

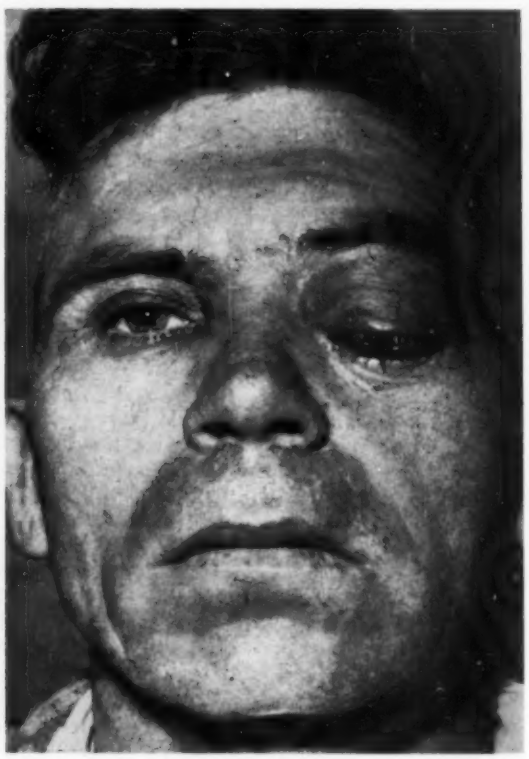

FIG. 652.—Orbital cellulitis as a complication of an ivory osteoma of the frontal air-sinus.

The operation may be used with some advantage in cases of chronic and acute infections of the sinus and for unilateral exenteration of the frontal and ethmoidal air-sinuses in cases of chronic catarrh.

ILLUSTRATIVE CASE

The patient was a man of 39 years of age. The history was that in July, 1953, his left eye began to water. A hard mass projecting downwards from the left upper orbital margin was detected by his general practitioner, Dr. Harrison. The patient was referred to the Department of Neurological Surgery on Sept. 1, 1953.

On examination, the left eyeball was found to be displaced downwards and forwards; there was, however, no complaint of diplopia, the movements of the eyeball being little impaired. The fundus of the eye was normal. Projecting into the orbit from its upper margin was a hard mass approximately ¾ in. in diameter. The skin moved freely over it. There was no clinical evidence of encroachment on the frontal fossa and no signs of compression of the brain. There was no swelling or disease elsewhere in the body. Radiography showed a dense mass in the left frontal region. A diagnosis of an ivory osteoma of the frontal air-sinus was made (*Fig.* 651).

In view of the encroachment on the orbit, removal of the growth was considered advisable. Before operation

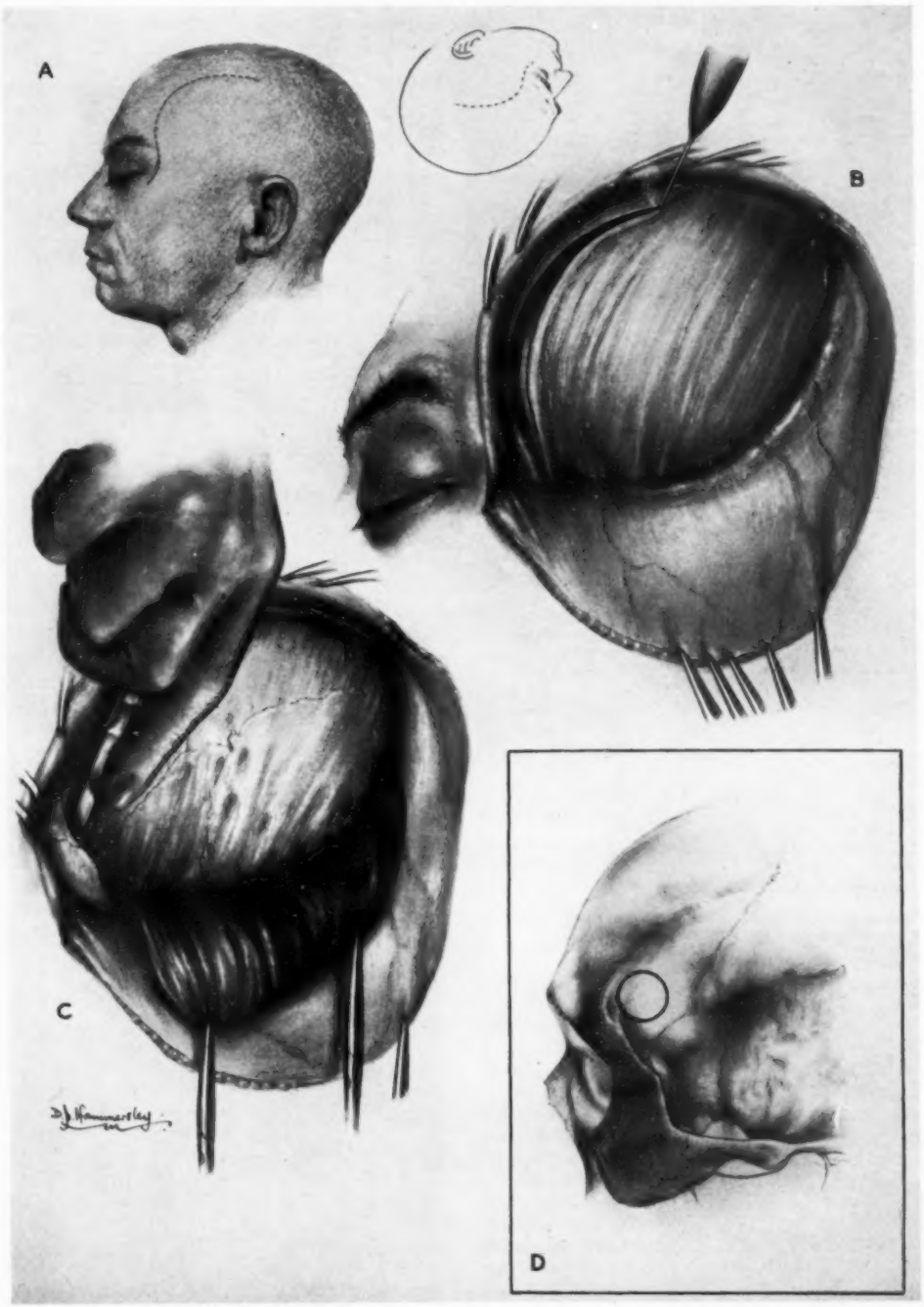

FIG. 653.—*Operative Technique*, 1.—A, Line of incision. B, Diathermy incision through attachment of temporal fascia. C, Reflection of muscle-flap and exposure of external angular process, malar bone, and part of temporal fossa. D, Site of burr hole exposure of dura of anterior fossa.

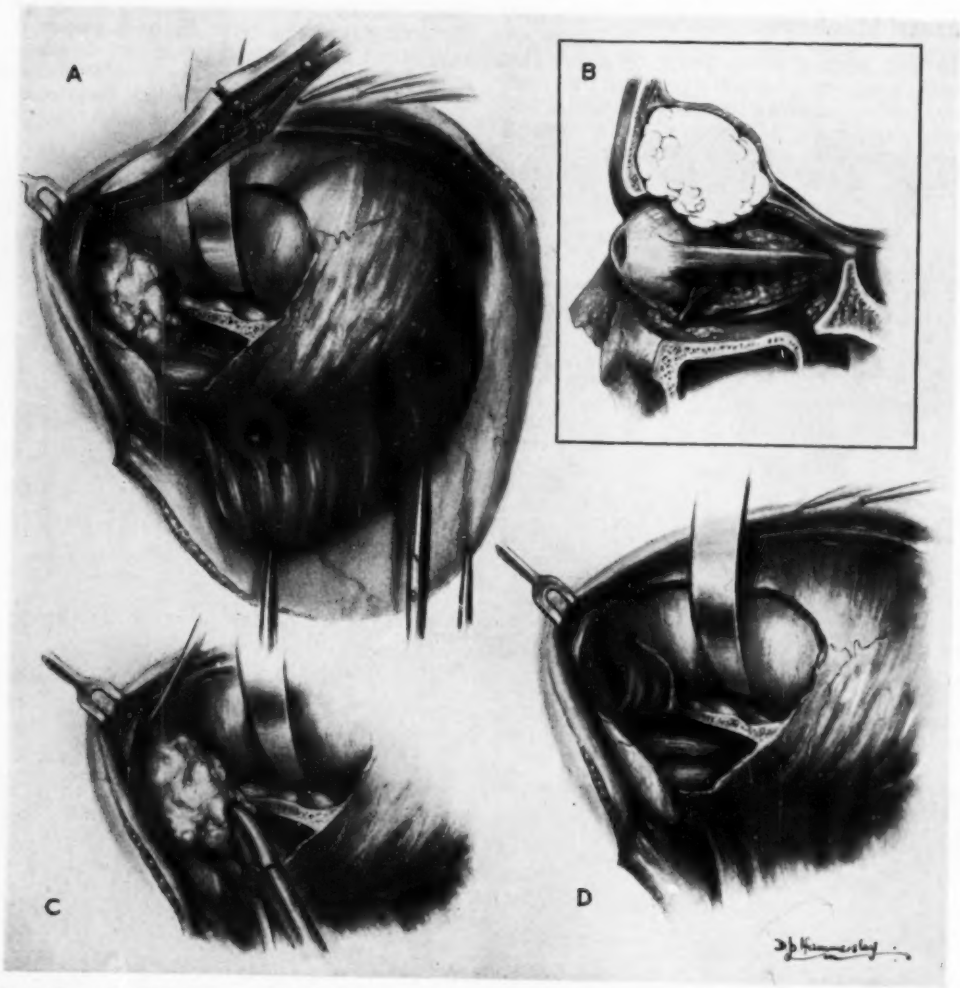

FIG. 654.—*Operative Technique*, 2.—A, The final exposure. B, Diagrammatic representation of relationship between osteoma and surrounding structures. C, Removal of the tumour. D, Structures at conclusion of operation and demonstration of view obtained of the frontal air-sinus.

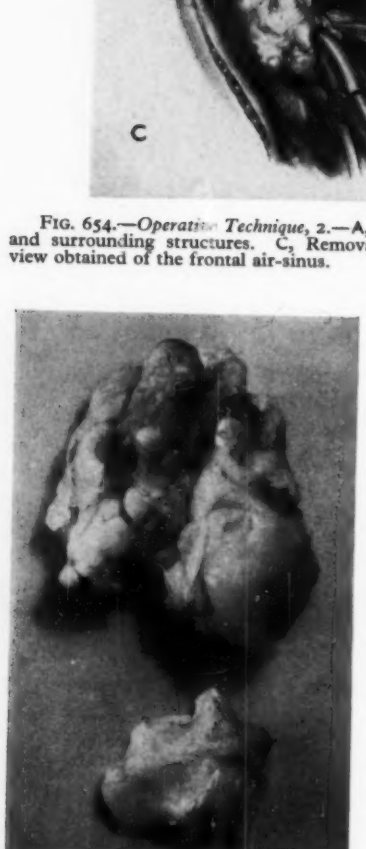

FIG. 655.—Clinical photograph showing the size and shape of the osteoma. (*Natural size.*)

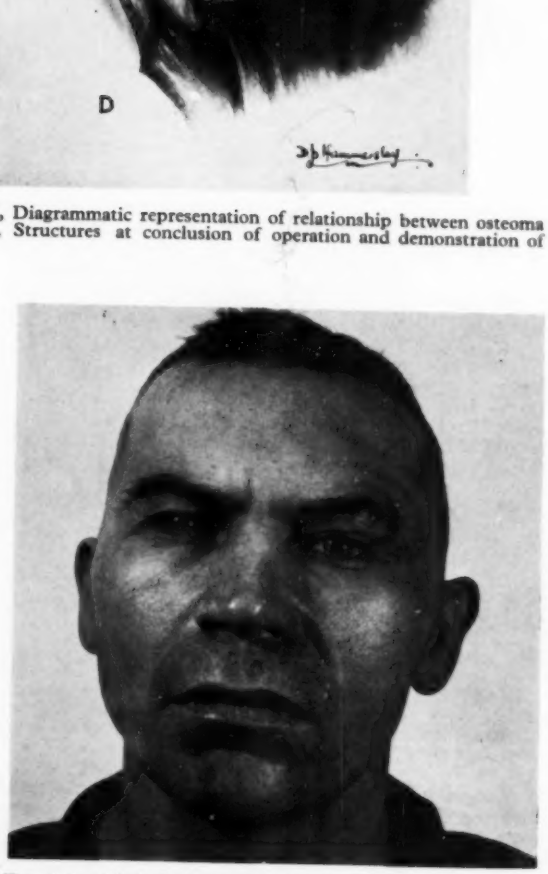

FIG. 656.—Clinical photograph showing post-operative result.

could be arranged, however, the eye suddenly became painful and there were signs of orbital infection, proptosis, chemosis, and œdema of the upper eyelid (*Fig.* 652).

The surgical problems were obvious; infection was already present; a large hard neoplasm had to be removed and the frontal lobe of the brain had to be protected from injury. The decision to operate was made in the belief that nothing short of complete removal of the tumour would meet the situation.

OPERATION (Oct. 10, 1953) (G. F. R. and P. R. R. C.).—The approach to the frontal air-sinus and tumour, we believe, is made clear in Mr. Hammersley's drawings (*Figs.* 653, 654).

By means of this exposure, a wide view of the interior of the sinus could be obtained, inspection of the dura and elevation of the frontal lobe of the brain was possible, and the orbit could be explored and drained. Once the osteoma was fully uncovered, it was easily rocked free from its bed, (*Fig.* 655).

There was low-grade infection in the frontal air-sinus and a fistula leading through the floor of the sinus into the orbit communicating with a small abscess cavity. The abscess was excised and tubes for the instillation of penicillin were inserted both into the frontal air-sinus and into the orbit. The wound was reformed in layers. Localized and general chemotherapy was instituted.

The result was satisfactory. The wound healed by first intention; the axis of the eye returned to its normal position; the infection subsided and the pain was relieved. From the photograph taken post-operatively, it will be seen how slight was the residual deformity following the operative procedure (*Fig.* 656).

PERFORATION OF MECKEL'S DIVERTICULUM BY FOREIGN BODY AND REVIEW OF THE LITERATURE

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BY the seventh week of intra-uterine life, when the embryo has attained a crown-rump length of 17 mm., the vitello-intestinal duct obliterates in approximately 98 per cent of cases. Failure of this and persistence of adventitious remains may give rise, as is well known, to diverse and usually unexpected surgical conditions at any time from infancy to old age. The ileal diverticulum, featured clearly in Ruysch's *Thesaurus Anatomicus* in 1701, was accurately described by Johann Friedrich Meckel in 1812 and has since been the object of wide surgical interest devoted to its manifold complications, of which perforation by foreign body would appear to be one of the rarest. The first case was described in 1899 by Blanc and a survey of the literature reveals that 26 cases only have so far been recorded (*Table I*). The present case is reported because it differs in many respects from the others.

CASE REPORT

Sapper J. B. J., aged 24, was admitted as a surgical emergency to the British Military Hospital, Tel-el-Kebir, on Sept. 16, 1951, at 11.30 p.m. He had been in perfect health until an hour previously when, while seated in a cinema, he was seized by a sudden and very violent, generalized, relentless abdominal pain, felt most acutely in the centre of the abdomen. He managed to stagger to a near-by toilet, where he was found in a collapsed state and sent to hospital. He had never had that pain before and could not recollect having had indigestion or attacks of pain in the right side of the abdomen. He felt nauseated but had not vomited. His bowels had been moving regularly and had opened that morning. He had never vomited 'coffee grounds' or passed 'tarry' stools. There had been no previous symptoms referable to any system or other illnesses except the exanthemata of childhood. Examination of his previous medical records confirmed his general good health.

ON EXAMINATION.—T. 100·4°, P. 90. Well-built patient with an anxious and suffering expression. Tongue coated. The abdomen was slightly distended and intensely and equally rigid in all quadrants. Pain on palpation was generalized, but more acute as the umbilicus was approached from the periphery of the abdomen. The navel itself, when gently pressed with the tip of the finger was, surprisingly, the most painful area of the abdomen, although it did not show any overt abnormality. There was clinically a small amount of free fluid, but no free gas. Rectal tenderness was present in the recto-vesical pouch, but no mass was felt. Examination of the other systems revealed that they played no causative part in this illness and a straight X-ray picture of the abdomen showed no abnormality.

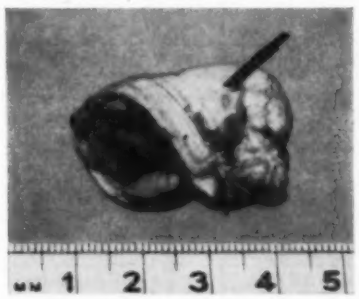

FIG. 657.—The excised Meckel's diverticulum showing the perforating wood splinter.

A diagnosis of generalized peritonitis due to perforated viscus was made and laparotomy performed one and a half hours after admission. Pre-operative intestinal intubation and drip infusion were started.

AT OPERATION.—Under general anæsthesia the abdomen was opened through a right paramedian incision. Turbid fluid was found in the greater sac. The appendix, stomach, and duodenum were not diseased. The small gut was inspected and a Meckel's diverticulum was found approximately 2½ ft. from the ileocæcal junction. A wood splinter had perforated the side of the diverticulum and protruded 15 mm. into the peritoneal cavity (*Fig.* 657), pointing backwards. The diverticulum was thickened by œdema and covered by a velum of fibrin. Its small mesentery was ligated and divided, the diverticulum was excised at its base between clamps, and the ileum closed transversely to its long axis by the Kerr-Parker method with two rows of Cushing's stitches. Appendicectomy was performed and the wound closed in layers with no drainage.

Table I.—SUMMARY OF CASES

No.	Author	Sex	Age	History	Physical Signs	Diagnosis	Perforating Object	Outcome
1	Blanc (1899)	M.	41	10 dy. intermittent pain in R.I.F. No vomiting	T. 104; P. 90. Rigidity of R.I.F.	Appendicitis	Fishbone	Laparotomy and recovery
2	Piquand and Grenet (1900)	F.	45	1 yr. intermittent abdominal pain, 8 dy. pain R.I.F.	T. 101·3. Rigidity in upper abdomen, jaundiced	?	Fishbone	Autopsy. Abscesses in abdominal cavity
3	Aschan (1909)	M.	42	5 wk. intermittent pain R.I.F., 2 dy. pain to right of umbilicus. Vomiting	T. 100; P. 90. Generalized rigidity, specially on the right side	Peritonitis due to appendicitis	Fishbone	Laparotomy and recovery
4	Scwenk and Pollnow (1912)	F.	21	Swallowed 2 gramophone needles 2 dy. previously. Abdominal pain in right side	T. 101·8; P. 100. Abdominal rigidity, specially to the right. Tender P.R.	Appendicitis due to F.B.	Gramophone needle	Laparotomy and recovery
5	Hagler and Stewart (1920)	M.	39	3 dy. intermittent abdominal pain. No vomiting	Guarding all over right side. Specially tender over appendix. W.B.C. 19,600	Appendicitis	Fishbone	Laparotomy. M.D. surrounded by omentum required bowel resection. Died
6	Henrichsen (1921)	M.	25	3 dy. history intermittent pain in R.I.F. Vomited	T. 100·4; P. 72. Tender to the right of the umbilicus. No rigidity	Appendicitis	Fishbone	Laparotomy and recovery
7	Lindqvist (1926)	M.	21	1 yr. intermittent R.I.F. pain, 2 dy. severe intermittent pain on right side	T. 101·4; P. 96. Tender and slightly rigid R.I.F.	Appendicitis	Wood splinter	Laparotomy and recovery
8	Berry (1927)	M.	36	30 hr. pain in R.I.F. No vomiting	T. 98·4; P. 90. Generalized tenderness of lower abdomen, most marked at McBurney's point. Tender P.R.	Appendicitis	Wood splinter	Laparotomy and recovery
9	Walkling (1931)	M.	8			Abdominal abscess	Fishbone	Laparotomy and recovery
10	Wilcox (1932)	M.	71	2 dy. intermittent lower abdominal pain and diarrhœa. No vomiting	T. 98·4; P. 78. Some resistance of R.I.F. W.B.C. 13,000	Appendicitis	Fishbone	Laparotomy and recovery
11	Hiller and Bernhard (1933)	M.	41	24 hr. pain to the right of umbilicus. No vomiting	T. 100·8; P. 108. Tenderness and muscular spasm R.I.F. W.B.C. 17,000	Appendicitis	Rolled tomato skin	Laparotomy and recovery
12	Bock (1933)	M.	7	1½ yr. intermittent abdominal pain to the right of the umbilicus. Hypospadias	'Slight' rise in temperature. Some increased resistance R.I.F.	? Congenital abnormality	Needle	Laparotomy and recovery
13	Webb (1933)	F.	15	6 hr. intermittent pain R.I.F.	T. 100; P. 72. Tenderness and rigidity R.I.F. W.B.C. 13,700	Appendicitis	Fishbone	Laparotomy and recovery
14	Fontaine and Bauer (1933)	F.	19	Swallowed knitting needle 14 dy. previously. Abdominal pain, no vomiting	T. 100·4; no abdominal signs	Arrested foreign body	Knitting needle with glass knob	Laparotomy and recovery
15	Donovan (1937)	M.	11	24 hr. pain in R.I.F. Vomited twice	T. 99·8; P. 100. 'Identical signs to those of acute appendicitis'.	Appendicitis	Wood splinter	Laparotomy and recovery
16	Persson (1939)	M.	75	Swallowed large fishbone 4 dy. previously. Stinging R.I.F. pain for 3 dy. No vomiting	T. 99·9; P. 80. Marked rigidity in R.I.F. No tenderness P.R. W.B.C. 12,000	Arrested fishbone	Fishbone	Laparotomy and recovery
17	Persson (1939)	M.	21	24 hr. intermittent right-sided abdominal pain. No vomiting	T. 100·2; P. 98. Slight guarding R.I.F. Tenderness medial to McBurney's point. P.R. tender	Appendicitis	Fishbone	Laparotomy and recovery
18	Persson (1939)	M.	18	Intermittent umbilical pain for many years. Generalized abdominal pain for 24 hr. No vomiting	T. 101·6; P. 96. Pain and slight rigidity at McBurney's point. P.R. not tender	Appendicitis	Wood splinter	Laparotomy and recovery

Table I.—SUMMARY OF CASES—*continued*

No.	AUTHOR	SEX	AGE	HISTORY	PHYSICAL SIGNS	DIAGNOSIS	PERFORATING OBJECT	OUTCOME
19	Williams (1940)	M.	62	Intermittent R.I.F. pain for many years. 3 dy. sharp stinging pains in R.I.F. No vomiting	T. 101·4; P. 96. Abdomen tender all over. Rigidity in R.I.F. W.B.C. 16,000	Peritonitis due to appendicitis	Fishbone	Laparotomy and recovery
20	Weinstein (1942)	M.	54	8 hr. pain round umbilicus and R.I.F. No vomiting. Appendicectomy 8 yr. previously	T. 99·2; P. 80. Moderate spasm of right rectus. W.B.C. 11,000	Intestinal obstruction	Fishbone	Laparotomy and recovery
21	Rossman (1943)	M.	17	36 hr. sharp intermittent pains in R.I.F. No vomiting	T. 98·4; P. 78. Slight muscular resistance R.I.F. and rebound tenderness P.R. tender. W.B.C. 14,000	Appendicitis	Fishbone	Laparotomy and recovery
22	MacFarlane (1948)	F.	21	6 dy. recurrent abdominal pain in upper and lower abdomen. No vomiting	T. 100; P. 96. Guarding and rigidity both iliac fossæ. Rovsing +. P.R. tender	Appendicitis	Cabbage stalk	Laparotomy and recovery
23	Seibert (1950)	M.	14	Few hr. pain in R.I.F. No vomiting	T. 98·6; some tenderness and rigidity at McBurney's point. P.R. tender. W.B.C. 18,200	Appendicitis	Fishbone	Laparotomy and recovery
24	McQuaid (1950)	M.	60	24 hr. circumbilical pain localizing in R.I.F. No vomiting	T. 98; P. 80. Hyperæsthesia, guarding and rebound tenderness in R.I.F. P.R. tender	Appendicitis	Rolled tomato skin	Laparotomy and recovery
25	Whelan (1951)	M.	70	2 wk. history of severe intermittent R.I.F. pain. No vomiting	T. 99; P. 84. Tender medial to McBurney's point, moderate rebound pain. W.B.C. 9200	Appendicitis	Fishbone	Laparotomy and recovery
26	Blomquist (1951)	F.	37	A few hours R.I.F. pain	'Physical signs suggestive of appendicitis'	Appendicitis	Fishbone	Laparotomy and recovery
27	Author's case (1951)	M.	24	One hour's sudden continuous generalized abdominal pain, referred to umbilical area. No vomiting	T. 100·4; P. 90. Board-like rigidity of abdomen. Extreme tenderness of umbilicus. P.R. tender	Perforated viscus	Wood splinter	Laparotomy and recovery

The post-operative period was uneventful; the patient was allowed to get up on Sept. 23 and was back with his unit on Oct. 10. The patient, on questioning, could not recollect having swallowed the splinter and could not account for its presence, nor did he wear dentures which might have reduced oral sensibility. The diverticulum was 30 mm. long, the diameters at its base were 25 mm. × 20 mm. The splinter measured 31 mm. and was 2 mm. wide.

DISCUSSION

Sex.—In a review of 5768 autopsies performed at a children's hospital, Christie (1931) found 63 cases of Meckel's diverticulum, an incidence of 1·2 per cent, and of these 74·6 per cent were males. It is therefore not surprising that 21 cases (77·7 per cent) out of the present series of 27 were of the male sex.

Age.—The youngest patient reported in this series was 7 years old, the oldest 75, and inspection of the intervening cases reveals that foreign-body perforations of the ileal diverticulum occur independently of age. As over 90 per cent of patients with Meckelian diverticulitis are under 30 years of age (Watt and Timpone, 1940), it would appear that foreign-body perforations occur independently of diverticulitis. This is in keeping with the pathological findings of Persson (1939).

Clinical Features.—Persson (1939), reviewing the symptomatology of 15 cases of foreign-body perforation of Meckel's diverticulum, stated that the onset was milder than in Meckelian diverticulitis, that perforation took place silently, and that symptoms of peritonitis were usually very moderate. Seibert (1950) pointed out that in these patients a typical perforation pain was lacking and that none presented the picture of an acute abdominal catastrophe, such as is witnessed in perforation of peptic ulcers. While this may be true in the majority of cases, sudden and very severe symptoms can nevertheless occur, as met in the author's experience.

The duration of symptoms leading to admission varied from fourteen days to one hour. Six patients had had chronic abdominal pains for periods ranging from five weeks to many years. The pain was recorded as intermittent in 16 case histories.

The site of pain was usually in the right iliac fossa, in 4 patients it was medial to McBurney's point and nearer to the umbilicus. When perforation occurred suddenly it was felt at the umbilicus. Vomiting was not a common feature and took place in 4 cases only.

The temperature was normal in 6 patients, elevated in all others. The right lower quadrant of the abdomen showed some guarding or rigidity in most instances and in 3 this was generalized. In 3 cases the area of maximum tenderness was near the umbilicus and in 1 case it was the umbilicus itself.

Diagnosis.—In 20 cases a diagnosis of appendicitis was made. This is not surprising, as a survey of the clinical histories reveals that the symptoms are in no way indicative of the underlying pathology. However, where the character of the pain was recorded, it was often intermittent and arising primarily in the right side of the abdomen, in contrast with appendicitis, where the pain is usually continuous once it has settled on that side.

Both Persson (1939) and Seibert (1950) stressed the importance in these cases of pain referred and elicited near the umbilicus. A case is here presented where the umbilicus, when tested for tenderness, was the most painful area of the abdomen, although the foreign body did not lie under it. This is interesting, as pain arising in a viscus supplied by autonomic nerves is often referred to a surface area which roughly corresponds to the embryonic position of that viscus. The umbilicus is not only the 'false localization' area of a diseased Meckel's diverticulum but also of the whole enterocolic loop, from the duodenal papilla to the splenic flexure of the colon.

Perforating Objects.—Sixteen of the perforations were caused by fishbones, 5 by wood splinters, 3 by needles, 2 by rolled tomato skins, and 1 by a cabbage stalk. In only 2 instances were the patients aware of having swallowed the foreign body.

Mortality.—Macmanus (1941) reported a 10 per cent mortality in 63 cases of intestinal perforations occurring between 1900 and 1940. Of the 27 cases of Meckel's perforations here assembled 2 died (7·4 per cent); one post-operatively owing to a leak at the suture line, the other was not explored and died while under investigation. Neither of these deaths occurred in recent years.

SUMMARY

1. Twenty-six cases of foreign-body perforations of Meckel's diverticula have been collected from the literature since 1899 and have been briefly reviewed, and a personal case has been described in detail.

2. Very sudden and severe symptoms, which hitherto were not considered a feature of this condition, are described.

3. In slow perforations, which are the commonest, the intermittence of the pain primarily arising in the right side of the abdomen, is stressed.

4. Maximal tenderness near the umbilicus or of the umbilicus itself should bring to one's mind the possibility of a diseased Meckel's diverticulum.

I should like to thank the Army Medical Directorate and Major-General A. J. Beveridge, Director of Army Medical Services, Middle East Land Forces, for permission to publish this case; and Professor Ian Aird for kind help and criticism.

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CARCINOMA OF THE HYPOPHARYNX AND UPPER ŒSOPHAGUS

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THE surgical problem which carcinoma of the hypopharynx and upper œsophagus presents is fully discussed in the papers of Wookey (1948), Bricker, Burford, and Eiseman (1949), and Raven (1952).

Surgical treatment should combine a wide resection of the tumour with an immediate reconstruction of the area, and restoration of swallowing.

The operative technique detailed below has proved of use in a patient with an extensive carcinoma of the upper œsophagus involving the larynx.

CASE REPORT

A 51-year-old female (1369/53) gave a history of nine months' dysphagia, progressive since September, 1953, and almost complete at the time of her admission at the beginning of December. She had also developed a cough when attempting to take liquids.

The only positive clinical findings were a palpable spleen and a smooth tongue. Her fingers were normal and there were no palpable enlarged glands in her neck or other significant findings. Her hydration was fairly

good. The white blood-count was 5100 per c.mm., hæmoglobin 70 per cent, colour index 0·85.

An X-ray examination with barium showed an almost complete obstruction of the œsophagus from the cricoid cartilage downwards for about 6 cm. and a marked increase in the gap between the trachea and the vertebral column at this level (*Fig.* 658).

At bronchoscopy on Dec. 3 under general anæsthesia the trachea and bronchi were normal. There was an irregular nodular mass of tissue spreading over the superior surface of the cricoid cartilage forward on to the posterior aspect of the larynx. The vocal cords were normal in appearance and function.

At Operation (Dec. 10).—Under general anæsthesia (Dr. Midgeley) with pentothal, curare, nitrous oxide, and oxygen, the patient was first placed in the right lateral position, and a left posterolateral thoracotomy made through the bed of the resected 8th rib.

The pleura was healthy and no tumour was palpable within the hemithorax. The diaphragm was opened and the only abnormality found within the abdomen was an enlarged spleen, which was about three times its normal size. The stomach was mobilized to just short of the pylorus by dividing the short gastric arteries and the left gastric artery at its origin and preserving the vascular arcades along the greater and lesser curvatures. The freeing of the gastro-œsophageal junction was carried out about 2·5 cm. from the œsophagus, leaving a cuff of diaphragm around the œsophagus. The œsophagus was mobilized from the diaphragm to the dome of the pleura. This was mainly completed by dissecting the surrounding

Fig. 658.—Radiograph of pre-operative barium swallow showing a long stricture of œsophagus and a trace of barium entering the trachea. The gap between the trachea and vertebral column is increased.

Fig. 659.—Posterior view of the resected specimen showing the œsophageal tumour involving 8 cm. of the œsophagus and spreading over the cricoid cartilage.

Fig. 660.—Anterior view of the resected specimen, showing the level of tracheal section anteriorly and the pharyngeal section superiorly.

structures and leaving the peri-œsophageal tissues intact. To complete the upper half of the dissection a short segment of the fourth left rib was resected.

The stomach was brought up to the lower border of the aortic arch and sutured in position there. The surplus œsophagus was drawn above the aorta and left there. The diaphragm was sutured around the stomach, a low intercostal drain was inserted, and the chest wall was closed in layers.

The patient was turned on to her back and a long collar incision was made in the neck. The pretracheal muscles were divided in the midline and thereafter clamped at the level of the upper border of the thyroid cartilage and divided. The two lobes of the thyroid were mobilized by dividing the middle and inferior thyroid veins and the inferior thyroid arteries. The

FIG. 661.—Photograph of the patient twenty-seven days after operation.

right lobe was dissected free of the trachea and left pedicled on the superior thyroid vessels; the upper part of the left lobe was freed and allowed to retract. It was believed that one of these portions of thyroid would include some parathyroid tissue. Thereafter the larynx and œsophagus were mobilized from the vertebral column. The trachea was divided below the 4th tracheal ring and the lower end was brought out through a second incision close to the sternum and re-intubated in this position. The larynx and œsophagus were turned up over the face and the intrathoracic œsophagus was brought up into the neck. The œsophagus was divided 5 cm. below the lower border of the tumour. The posterior wall of the pharynx was incised and sutured to the posterior œsophageal wall with a single layer of interrupted sutures. The pharynx was excised just below the hyoid bone and the pharyngo-œsophageal anastomosis was completed. During the making of the anastomosis the œsophagus remained normal in colour and there was some bleeding from its cut surface.

The pretracheal fascia and muscles were sutured together in the midline and along the line of the lateral incisions which were made earlier. The wound was closed without drainage.

At post-operative bronchoscopy, through the tracheotomy, there was a little blood-stained mucus in the upper bronchi.

THE SPECIMEN.—Examination of the resected specimen showed the œsophageal tumour to be 8 cm. in length (*Figs.* 659, 660). The tumour was a well-differentiated squamous carcinoma and there was no evidence of distant spread.

PROGRESS.—The only complication of the post-operative course was difficulty in micturition due to inadvertent overdistension of the bladder during the second post-operative night.

FIG. 662.—Radiograph of barium swallow after operation, showing the pharyngo-œsophageal anastomosis at the level of the hyoid bone.

Fluids were started by mouth on the second post-operative day, when bowel sounds had returned. Semi-solid foods was started on the tenth post-operative day. The patient was by then complaining of severe hunger. She resumed a normal diet fourteen days after the operation.

Fig. 661 shows the patient 27 days after operation and *Fig.* 662 shows the pharyngo-œsophageal anastomosis outlined with barium.

CONCLUSION

This operation has shown that in a relatively young patient the blood-supply of the lower half of the divided œsophagus can be adequately maintained from the right gastric and right gastro-epiploic vessels via the stomach, and this portion of the œsophagus can be used to reconstruct more proximal portions of the intestinal tract.

Further operative experience with the technique is necessary to determine the extent of usefulness of the procedure.

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TWO CASES OF THORACOPAGOUS TWINS

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"AMONG all the wealth of observation and the multiplicity of forms, there are still lacunæ in our knowledge which time may perhaps fill up. Every double monster is well worth dissecting." (Ballantyne, 1904.) This advice is especially applicable to-day in view of the advances in surgical technique and the recent attempts to separate thoracopagous twins, the commonest type of double monster. Not only should the surgeon be aware of the enormous variation in visceral union which may exist, and be capable of recognizing the abnormalities during life, but he must always remember that congenital abnormalities confined to one twin and incompatible with a separate existence by that twin may also occur. Since thoracopagous twins are not as common as to allow one person to investigate a large number, all dissections of these monsters should be recorded.

FIG. 663.—*Case* 1. Human thoracopagous twins.

Fig. 663 shows a case of human full-time female thoracopagous twins. The late Professor A. Low noted on receipt of the specimen ". . . the total weight is 11-lb. and the lengths 18½-in. and 16-in. . . . The umbilical cord is somewhat strap-shaped, ¾-in. wide by ½-in. thick, and contains two veins and three arteries. The placenta has much the appearance of an ordinary uniovular placentation".

The upper half of the body of the sternum in the larger twin (A) is normal, but its lower half and the whole of the body of the sternum in the smaller twin (B) are longitudinally divided, the left half of one fused with the right half of the other. Above the large umbilical hernia, the anterior abdominal wall is continuous from one twin to the other. The other visceral abnormalities are shown in *Fig.* 664. The two hearts lie in a common pericardial cavity; the apex of heart (A) points to the right so that its left atrium is opposed to the right atrium of heart (B) and communicates with it by a wide channel. In addition to the normal right superior vena cava there is a left superior vena cava entering the left atrium of each twin. Twin (A) provides two umbilical arteries, twin (B) one artery; the two umbilical veins are on the same side of the specimen. The livers, lying below a common diaphragm, are both rotated to the right and their visceral surfaces are partly fused with one another. The stomach and upper part of the duodenum in each, hidden by the livers and slung from a common lesser omentum,

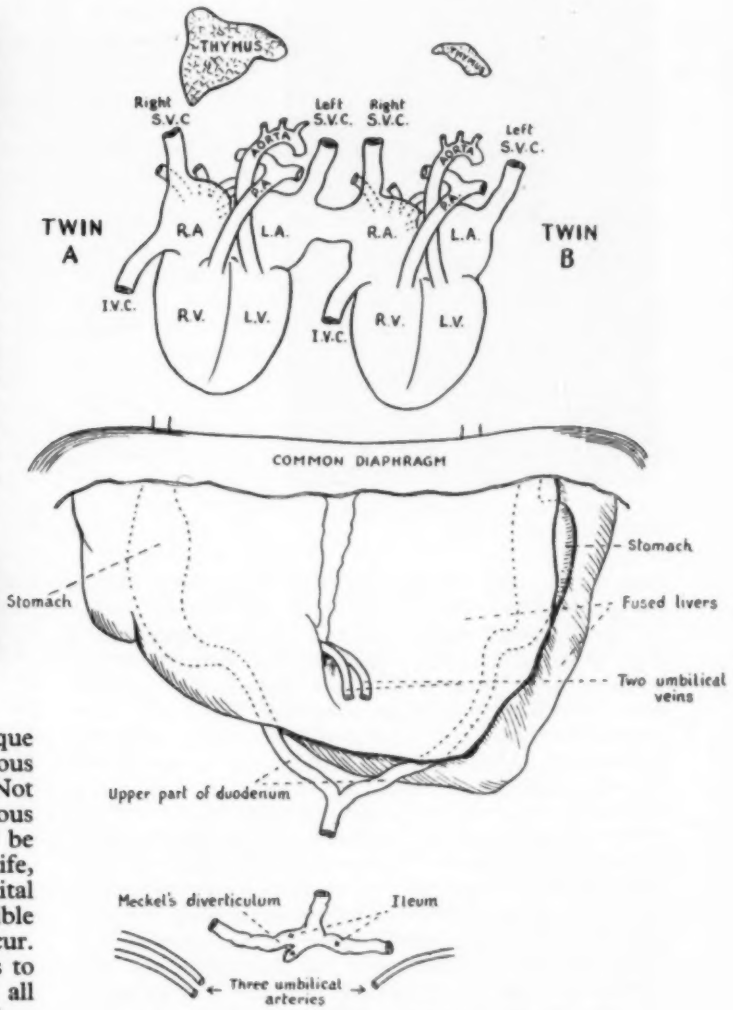

FIG. 664.—The visceral abnormalities found in *Case* 1.

can be traced into a common lower duodenum and thence into a common jejunum and ileum as far as a single Meckel's diverticulum; thereafter each twin has its own intestinal tract. The thymus in twin (A) is normal in size and position, but that of twin (B) is very small, and both suprarenal glands are normal.

FIG. 665.—*Case* 2. Thoracopagous twin pigs.

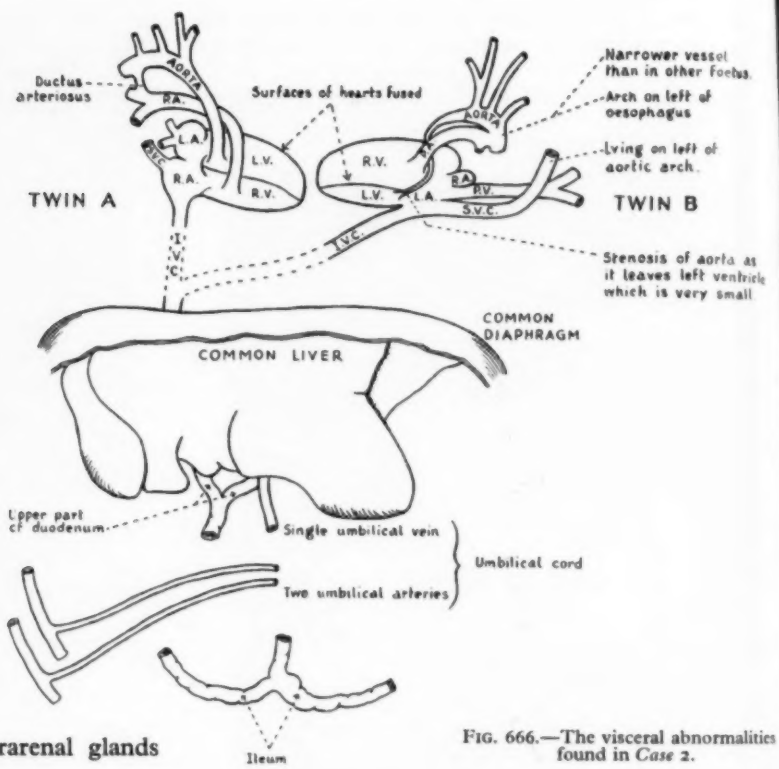

FIG. 666.—The visceral abnormalities found in *Case* 2.

The second case, full-time thoracopagous twin pigs (*Fig.* 665) which survived for 5–6 hours, resembles the human twins in the degree of fusion, but only superficially because even the sterna are more extensively involved, the manubria alone escaping fission and fusion with one another. *Fig.* 666 shows the abnormalities found on dissection; a single umbilical vein carries blood to the whole of the liver, which shows no evidence of ever having been two separate organs. The venous drainage of liver and abdomen through the common diaphragm is via a short single inferior vena cava lying entirely within twin (A); immediately before entering the right atrium of this twin, the inferior vena cava divides to send blood to both hearts. The presence of two hearts is recognizable but only on close examination; it appears as if the apex of each has been pulled ventrally and then the diaphragmatic surfaces applied and fused to one another, leaving only faint indication of the union. The chambers and main arterial and venous trunks of heart (A) are normal, but not those of heart (B); its 'inferior vena cava' looks like a prolongation of the *left* atrium drawn out below and between the two hearts to tap the inferior vena cava of the other twin. In twin (B), the superior vena cava, approaching on the left of the aortic arch and in front of the root of the left lung, also drains into the left atrium. The pulmonary veins reach the heart close behind this vessel, but whether they enter the left or right atrium is impossible to decide because there is no sign of an interatrial septum and only a very small right auricular appendage hidden behind the right ventricle is recognizable. The large right ventricle leads into a wide pulmonary trunk, while the diminutive left ventricle had obviously no function because the aorta is completely stenosed at its origin and has only a narrow lumen as far as the ductus arteriosus. Here most of the blood was diverted into the aortic arch and distributed to the systemic circulation. During fœtal life the only route from the twins to the placenta was through the two umbilical arteries which arise from twin (A). There is none from twin (B).

If the human twins described here had survived, heroic surgical procedures may have succeeded in separating them—in fact similar cases may yet be separated—but no surgery could have been of avail in the case of the pigs, where the two circulations were so inextricably intermingled and abnormal.

SUMMARY

The abnormalities found in two cases of thoracopagous twins are described, with special reference to the possibility of separating the twins surgically.

I am indebted to Professor R. D. Lockhart for his guidance and helpful criticism during the preparation of this paper.

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EXPERIMENTAL SURGERY

THE INTERPRETATION OF BIOCHEMICAL EFFECTS OF INJURY AND ISCHÆMIA

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FROM the earliest ages of history man has been interested both in the production and in the treatment of wounds. In the dawn of the historical period the Edwin Smith Papyrus shows that the study of wounds had reached an advanced stage, and their treatment was based on sound principles. This pre-occupation with wounds and the wounding agent has always drawn man's attention to the local nature of the wound and to the local response to the injury process. The studies of the last century have been concerned chiefly with the morphological changes in the tissue at the site of injury and of the sequelæ, especially infection. The fascination of the vascular reaction, the phagocytic infiltration, the fibroblastic proliferation, and the growth of new capillaries into the damaged tissue—in short, this dynamic counteraction to trauma—has perhaps blinded us to the more generalized response of the body metabolism which takes place. In particular, the early development and the rapid strides made in bacteriology, have directed medicine along a path which, no matter how productive it may have been in the past, has led us away from the study of body metabolism.

The gradual application of metabolic experiments to the problems of trauma have indicated that the body makes a general metabolic as well as a local response to injury, the nature of which is apparent only in outline at the present time. In 1872 Bauer observed an increased excretion of nitrogen after hæmorrhage, and in 1904 Hawk and Gies confirmed this, showing also that the actual operation of venesection without the withdrawal of blood was sufficient, in the dog, to cause an increased urinary output of nitrogen and sulphur. It is, however, from the experiments of Cuthbertson and his associates (Cuthbertson, McGirr, and Robertson 1939; Cuthbertson, 1942) that modern work in this field has stemmed. They showed that, as a result of operative fracture of the long bones in rats, a well-marked loss of nitrogen, phosphorus, and potassium in the urine occurred. That potassium was lost during the phase of negative nitrogen balance suggested that they were both derived from the destruction of tissue cells. If indeed they were both mobilized from autolysed cells, for each 1·0 g. of nitrogen lost, 13 mg. of potassium would also be lost. Cuthbertson pointed out, however, that the potassium loss was far greater than could be accounted for by local tissue injury, and that the potassium : nitrogen ratio was greater than their relative proportions in tissue cells. This implied that, in the case of potassium at least, a more generalized cellular loss had resulted from the injury. In 1939 Wilson and Stewart also noted that, in experimental burns, sodium was lost from the extracellular fluids into the cells of the damaged tissues and also into the erythrocytes of the general circulation. In the study of injuries sufficiently severe to produce shock, Fox (1944) showed that effective electrolyte replacement therapy required a volume of sodium-containing fluid in excess of the loss at the site of injury. Further, in experimental studies on shock (Fox and Baer, 1947) it was shown that injured tissues contained more sodium than that present in the interstitial fluid. That a phase of negative nitrogen balance follows operation in the human was confirmed by Wilkinson, Billing, Nagy, and Stewart (1949), who also showed that this was associated with sodium chloride and water retention. The same workers (Wilkinson and others, 1950) also observed a phase of increased potassium excretion in the urine in the early post-operative period. They suggested that these changes were due to a loss of potassium from the tissue cells at the site of injury, and the accumulation of sodium chloride and water in the interstitial compartment of the damaged tissues. These patients, however, were undergoing major surgical operations, and the changes detected may have been influenced by blood and secretion losses which were not studied as in a balance experiment. The dislocation of the body hydrodynamics brought about by major operation and post-operative treatment may be so great as to obscure the basic changes associated solely with the injury. Finally Howard and Carey (1949) and Darrow and Pratt (1950) have also drawn attention to a phase of sodium chloride retention in the immediate post-operative phase. It seems possible, therefore, that in man, the dog, and the rat, injury or operation is associated with a phase of increased nitrogen and potassium elimination, associated with a retention of sodium, chloride, and water. This pattern of nitrogen and electrolyte changes would appear to form part of the general response to injury. The cause of these electrolyte changes requires some further explanation.

Electrolyte Changes and the Role of the Adrenal Cortex.—It was first known from the work of Thomas Addison (1855) and Brown-Séquard (1856) that the adrenal glands were necessary to life, but it was not until 1923 that Houssay and Lewis

*Aided by a grant from the Medical Research Council.

demonstrated that it was the cortex which was the life-preserving factor. Swingle and Pfiffner (1930) isolated a lipid-soluble fraction which prolonged the life of the adrenalectomized animal and Weil and Browne (1939) showed that this 'cortin' appeared in the urine during the convalescence from acute

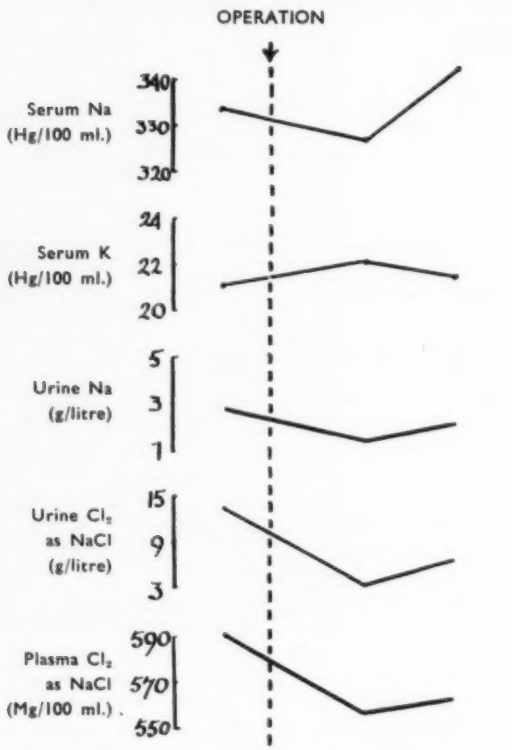

FIG. 667.—Changes in blood and urinary electrolytes associated with simple operation.

influenza. It has been known from the work of Cannon (1929) that the secretion of the adrenal medulla had a very considerable part to play in the conditioning of the animal to fear, rage, and to injury. It now began to be evident that the adrenal cortex exerted a different, but no less important type of influence on the body following trauma. The literature and the theories which have developed on the function of the adrenal cortex in response to injury have grown rapidly in the last decade. The concept of the place of the adrenal cortex in the adjustment to the environment has, however, owed such a debt to the work of Hans Selye that he must be considered the founder of the current views. The views of Selye (1950) are not shared by all, and even those who subscribe to his main thesis cannot agree with him in all the ramifications of the 'general adaptation syndrome'. It is not proposed to discuss these views here, but simply to record the fact that to Selye we owe the concept that the body makes a generalized response to illness and to injury and that the adrenal cortex has some part to play in this response.

It is known that deoxycorticosterone acetate (DOCA) induces a renal reabsorption of sodium chloride and water (Thorn, Howard, and Emerson, 1939), and it has been shown more recently that 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone (cortisone) also possess this saline-retaining property, though in less degree (Ingle, 1950). Selye and Dosne (1941) also noted this chloride retention in animals following injection of deoxycorticosterone acetate, and a reduction in plasma-chloride, if this had previously been normal.

The similarity of these electrolyte changes to those encountered in association with injury led many to suggest that the changes were in fact due to an increased cortical adrenal function. The very nature of disease, the frequent association of operation with other abnormalities and deficiencies of electrolyte and water, and the lack of 'balance' technique, however, render some of these observations valueless. It should be appreciated that blood-electrolyte estimations, expressed in concentrations, are no reflection of total body content, unless the blood-volume, extracellular fluid volume, and total body water are known, or else unless steps are taken to reduce changes in body water to a minimum. In such studies on minor operations (MacPhee, 1953), the sodium chloride and water retention and increased potassium loss were observed, and they were associated with a diminution in circulating eosinophils by 50 per cent, an increased 17-ketosteroid excretion, and a rise in fasting blood-sugar, all inferential evidence of increased adrenal cortical function. *Fig.* 667 illustrates typical findings in a patient subjected to a simple repair of an indirect inguinal hernia. In spite of the sodium chloride retention, however, it was noted that the plasma concentrations of sodium and chloride were diminished after these minor operations. This was observed previously by Annersten and Norrinder (1946), but they considered that the reduction was not significant. The excellent study of Moore and Ball (1952) on a large series of patients confirmed all these findings, and they also drew attention to this slight fall in the extracellular concentration of sodium and chloride during this phase of salt retention. It would seem that this effect could be the result of a relatively greater water than sodium retention, which would seem improbable, or of a disappearance of sodium and chloride in greater proportion than water from the extracellular phase.

A similar general sodium retention and increased potassium excretion after operation has been observed by Le Quesne (1953), who suggested this was in part due to an increased adrenocortical activity, but that some of the water retention resulted from an increased secretion of pituitary antidiuretic hormone. No direct evidence of this has so far been presented. However, knowledge of the electrolyte exchanges between tissue cells and tissue fluid has undergone considerable extension in recent years, and a brief description of the evidence upon which modern views are based must now be considered.

Cellular Electrolyte Exchanges.—The older concept that potassium was not only the chief, but the sole intracellular cation is now known to be

mistaken. Mullins, Fenn, Noonan, and Haege (1941) have demonstrated the rapid penetration of the erythrocyte not only by radio-active potassium, but also to a lesser extent by sodium, in three hours. During anaerobic metabolism, in the absence of glucose, the potassium concentration of the serum (Danowski, 1941) or the brain tissue fluid (Dixon, 1949) has been shown to increase, owing to a loss of potassium from the cells. Maizels (1949) has shown that, in stored blood, an active expulsion of sodium from the cell takes place, accompanied by an uptake of potassium. The energy for this process is supplied by glycolysis. In isolated liver slices, the retention of potassium is dependent on normal aerobic metabolism (Flink, Hastings, and Lowry, 1950). It seems apparent therefore that, in the presence of adequate oxygenation and adequate energy supply, potassium accumulates in tissue cells, and the sodium which also enters is expelled. In the study of isolated tissues where oxygenation is deficient, potassium leaks out from the cells. However, the relative cation content of the cells is dependent also on other factors. In animals on a low-potassium, high-sodium diet, a partial replacement of deficient cellular potassium by sodium occurs (Heppel, 1939; Miller and Darrow, 1940). This has also been noted under certain circumstances in alkalosis (Gamble, Fahey, Appleton, and Maclachan, 1945; Darrow, 1945). Deficient potassium intake, and alterations in the chemical nature of the cell environment, therefore, may also lead to a loss of potassium from, and an accumulation of sodium in, the cell. In addition, Ferrebee, Parker, Carnes, Gerity, Atchley, and Loeb (1941) have clearly shown that in dogs symptoms of cellular depletion of potassium may arise following the administration of deoxycorticosterone acetate (DOCA). They produced muscular weakness and paralysis, associated with a partial replacement of intracellular potassium of skeletal muscle by sodium. It seems possible, therefore, that the adrenal cortical secretion may also have a similar effect on the balance of cation within the cell.

THE NATURE OF THE PRESENT INVESTIGATION

The foregoing observations suggest that there is an increased adrenocortical activity as a result of, or in association with, operation or injury, and that the electrolyte changes in the urine are consistent with this increased activity. The potassium loss has not, however, been traced to the cells, nor is there conclusive evidence of an increase in the sodium content of the fixed tissue cells. In the experiments of Fox and Baer (1947) severe shock was a prominent feature. The nature of surgical shock is so ill understood, and the fluid and electrolyte changes are so complex, that it is difficult to separate primary from secondary results. An accumulation of sodium in the damaged limb has been observed in rabbits subjected to severe frostbite (Crismon and Fuhrman, 1946). The same workers, Fuhrman and Crismon (1951, a), observed, after the release of a tourniquet, an accumulation of sodium and water in, and a loss of potassium from, the damaged rat limb. They noticed similar results after vascular occlusion of the limb by glass microspheres (Fuhrman, Watson, and Crismon, 1951) and after the intra-arterial injection of thiopentone (Fuhrman, 1951). For present consideration, however, the most important paper is that in which the early and late results of tourniquet occlusion in limb muscle is studied (Fuhrman and Crismon, 1951, b). The results show that in periods varying from 1 hour to 144 hours after the release of a tourniquet (previously applied for 2 hours) there is an increase in total water and total sodium and a diminution in total potassium in the damaged limb as compared with the contralateral undamaged limb. These changes were reversible. Similar, but more marked and irreversible changes, were observed after the release of a tourniquet applied for 4 hours. These experiments, however, measure primarily the total and not the cellular cation, and, in addition, the contralateral undamaged limb is used as the term of reference. If, however, changes of a minor degree are occurring in association with injury in this undamaged limb, they cannot be detected by these experiments.

The Biological Implication of Anoxia.—Experiments in rats similar in nature to those of Fuhrman and Crismon have been carried out by us and the detailed results are published elsewhere (MacPhee, 1955). In order to obtain a direct mensuration of the cellular cation, the interstitial muscle water was estimated by using a thiocyanate technique, and the cation content calculated from serum concentrations. Before injury by the tourniquet, a biopsy specimen of abdominal muscle was taken and used as the normal pre-tourniquet specimen for that animal.

The results show that, after the application of a tourniquet sufficient to obliterate the arterial circulation in the rat's hind limb, and before the tourniquet has been removed, the intracellular sodium-to-potassium ratio remains unaltered. Two hours after the removal of the tourniquet, however, sodium passes into the cell and potassium is lost from the cell. This happens also in the tourniquet limb in adrenalectomized rats. Twenty hours after the tourniquet has been removed, the muscle cell is nearly depleted of potassium, and the sodium content very considerably increased. Forty-four hours after the tourniquet has been removed, similar though rather less marked, changes are found. In addition, as would be expected, a considerable increase in interstitial water (œdema) occurs, but there is evidence to show that an increase in intracellular water has also taken place. The potassium derived from the cells has therefore not been associated with a cellular dehydration.

The application of a tourniquet in the manner described for four hours would lead to a degree of ischæmia sufficient to produce cell necrosis. Two hours after the tourniquet is removed interstitial œdema is evident and the separation of the muscle-fibres can be seen in *Fig.* 668. Ten days after the removal of the four-hour tourniquet, although total gangrene has not been encountered in this series, cell death is obvious, the muscle being infiltrated with young fibrous tissue. The muscle cells which persist are obviously dead (*Fig.* 669). Similar observations were made by Fuhrman and Crismon, but they showed that the cation changes after the removal of a two-hour tourniquet were reversible, whereas they were not

after a four-hour tourniquet. Such, indeed was also our experience in the present investigation. It seemed to us, therefore, that cell death might be detected at an early stage by these cation changes before morphological evidence of tissue destruction and increase in cell sodium was detected in the contralateral undamaged leg, though these changes were not nearly so marked as in the ischæmic limb. In the adrenalectomized animals, no such changes were encountered and any changes detected could

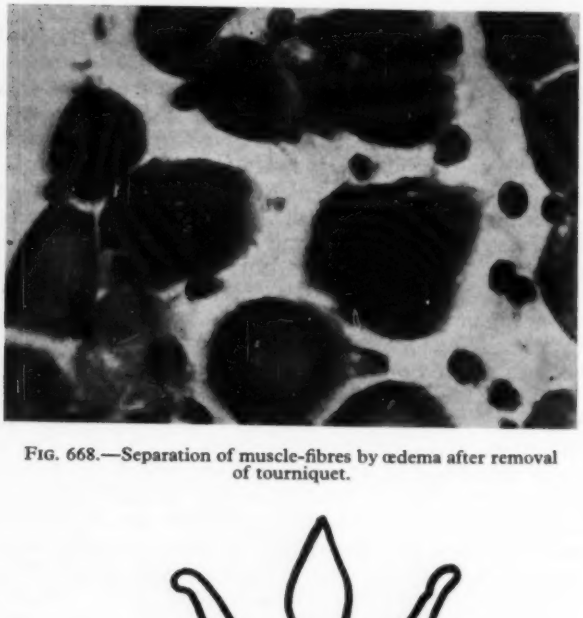

FIG. 668.—Separation of muscle-fibres by œdema after removal of tourniquet.

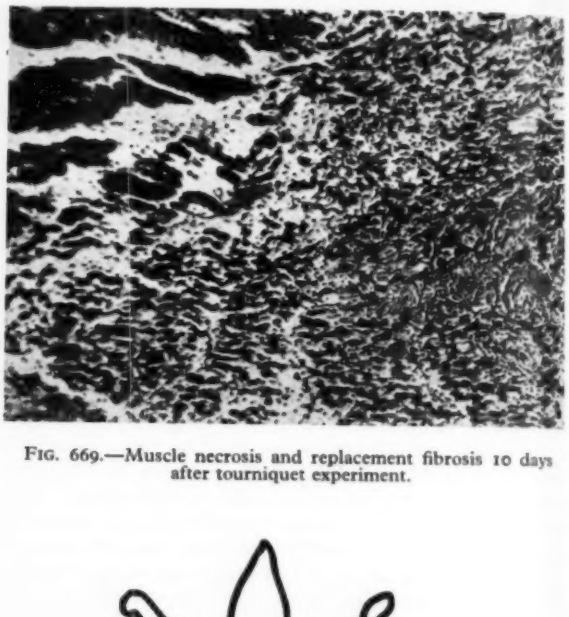

FIG. 669.—Muscle necrosis and replacement fibrosis 10 days after tourniquet experiment.

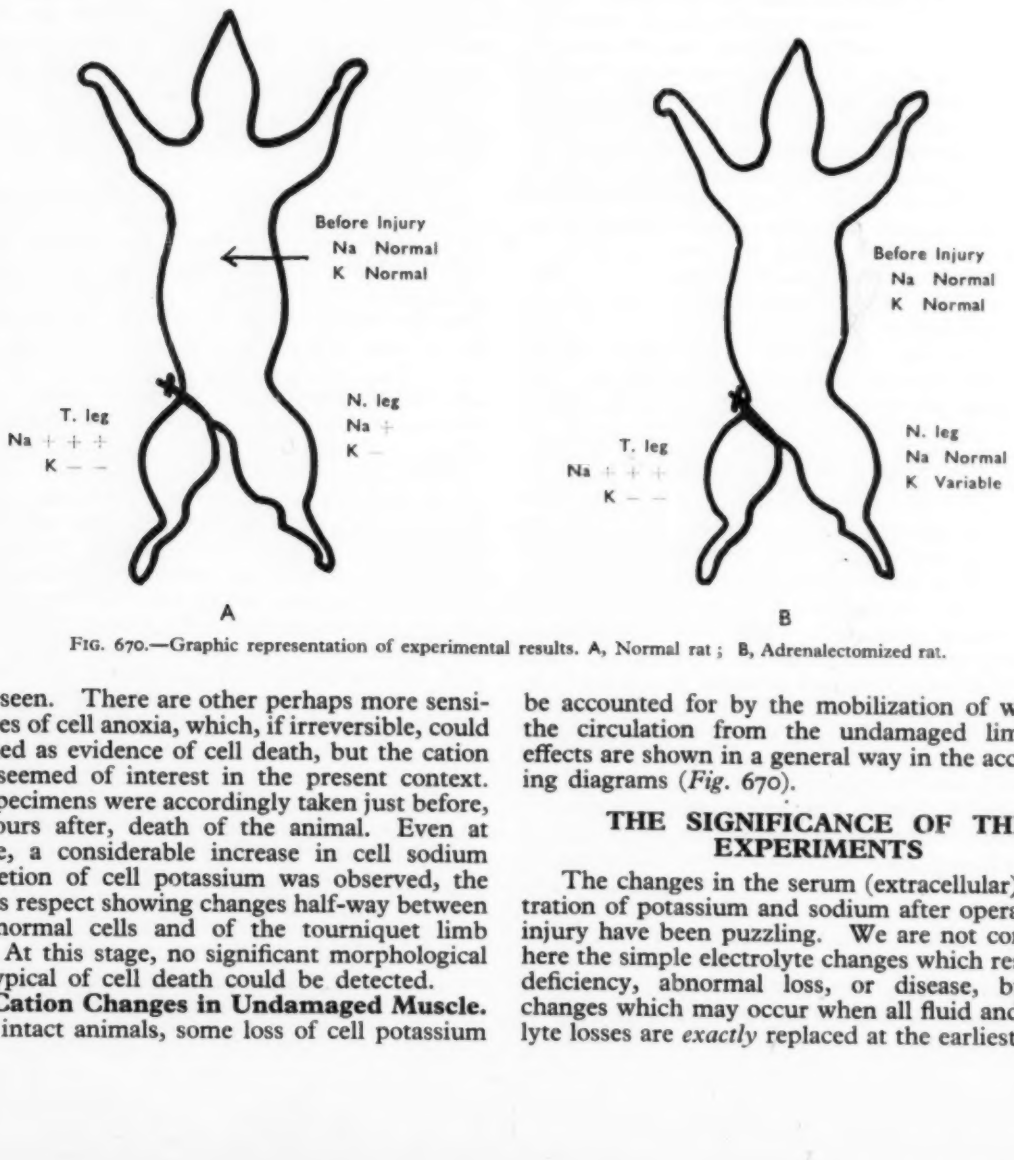

FIG. 670.—Graphic representation of experimental results. A, Normal rat; B, Adrenalectomized rat.

could be seen. There are other perhaps more sensitive indices of cell anoxia, which, if irreversible, could be assumed as evidence of cell death, but the cation changes seemed of interest in the present context. Muscle specimens were accordingly taken just before, and 2 hours after, death of the animal. Even at this stage, a considerable increase in cell sodium and depletion of cell potassium was observed, the cell in this respect showing changes half-way between that of normal cells and of the tourniquet limb muscle. At this stage, no significant morphological change typical of cell death could be detected.

The Cation Changes in Undamaged Muscle.—In the intact animals, some loss of cell potassium be accounted for by the mobilization of water into the circulation from the undamaged limb. The effects are shown in a general way in the accompanying diagrams (*Fig.* 670).

THE SIGNIFICANCE OF THE EXPERIMENTS

The changes in the serum (extracellular) concentration of potassium and sodium after operation and injury have been puzzling. We are not considering here the simple electrolyte changes which result from deficiency, abnormal loss, or disease, but those changes which may occur when all fluid and electrolyte losses are *exactly* replaced at the earliest possible

moment. In particular, blood studies in surgical shock have always been difficult to understand. Scudder (1940) first drew attention to a terminal rise in (extracellular) serum-potassium in shock; a rise which he considered might be the cause of death. This terminal rise in potassium concentration has since been discounted by many, but its exact significance has not been considered. Though true irreversible oligæmic shock was not being studied in the present experiments, it seems clear that an anoxic state, especially in damaged muscle, is associated with the transudation of potassium from the cell to the extracellular phase. If the peripheral circulatory failure is such that renal function is impaired, and excretion is negligible (as it is in serious shock), then this potassium accumulates in the extracellular fluid, and toxic concentrations are rapidly built up. This increased potassium concentration in the blood is clearly a reflection of the severity of the tissue anoxia and the tissue damaged, and is not, surprisingly enough, evidence of impending death. Indeed, after death, the extracellular potassium concentration continues to increase, in the rat at least, to 100 milli-equivalents or more per litre. It seems possible, also, though the matter requires further study, that water and sodium are not only lost from the circulation into the interstitial spaces of the damaged tissues, but also into the cells of the damaged and anoxic tissues. The familiar studies of Blalock (1930) and his conclusion that sufficient fluid is lost into the damaged tissues to account for the oligæmia of this type of shock may, in part, be a reflection of cellular as well as extracellular water and salt accumulation. It may perhaps be for this reason that raising the osmotic tension in the circulatory compartment with plasma or artificial macromolecular solutions is sometimes insufficient to withdraw the exudate from the damaged tissue. The return of sodium and water from the cells is a rather slower process than from the extracellular space, and in the rat appears to take about 72 hours before it is complete. In effect, the continued leakage of water, protein, and electrolyte into the damaged tissue spaces may be made more serious by the passage of water and electrolyte at least, into damaged cells, where, for the time being, they are not only lost but temporarily beyond recall.

The significance of the rather less marked changes in undamaged muscle is difficult to interpret, but the changes appear to be due to or governed by cortical adrenal activity. That the adrenal cortical hormone or hormones induce a retention of sodium chloride and water and an increased excretion of potassium we know, and that this positive balance of sodium and water cannot be detected in the extracellular compartment *in the early stages*, we also know. If, in fact, some sodium and water accumulates in the normal cell, the purpose of this is not evident at this stage. It seems safe to suggest that this sodium accumulation and potassium loss from the undamaged muscle cell when another part of the body is injured, is merely incidental to adrenocortical activity, which, in some entirely different respect, conditions the body to make a response to injury. The nature of this response and its importance in the ultimate survival of the animal is quite unknown at the present time. We are now, however, in a position to trace the potassium loss from the cell after injury, we know its meaning and its significance, and we are better prepared to interpret it in the course of routine surgical practice.

CONCLUSIONS

1. The retention after operation or injury of sodium and chloride and a corresponding amount of water is recognized. These electrolytes should, therefore, be administered only in proportion to their pre-operative deficiency or post-operative loss.

2. The absence of sodium chloride from the urine in the first post-operative week is no indication of the internal economy and is not evidence of salt deficiency.

3. The electrolyte changes in surgical shock have always been puzzling. It is now apparent that the serum concentrations are a reflection not only of the extracellular concentration, but of the transference of ions into and out from the cell.

4. The loss of fluid and electrolyte not only into the tissue spaces but into the cells, both damaged and undamaged, may account for some of the features of irreversible shock.

5. Where renal function is impaired the mobilization of potassium from the cells may lead to toxic concentrations of potassium in the serum. This is a result of tissue damage and, although related to shock, does not appear to be its dominant feature.

We are grateful to Professor Wells for his advice during the course of this work, and to Mr. J. Pike and Mr. J. Clark for their technical assistance. The photomicrographs are by Mr. W. Lee, of the Photographic Department, University of Liverpool.

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THE TRANSPLANTED ADRENAL GLAND

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THE surgeon's interest in the adrenal gland is becoming deeper and the mode of its regeneration occupies an important place at the moment. The technique of transplanting adrenal glands involves

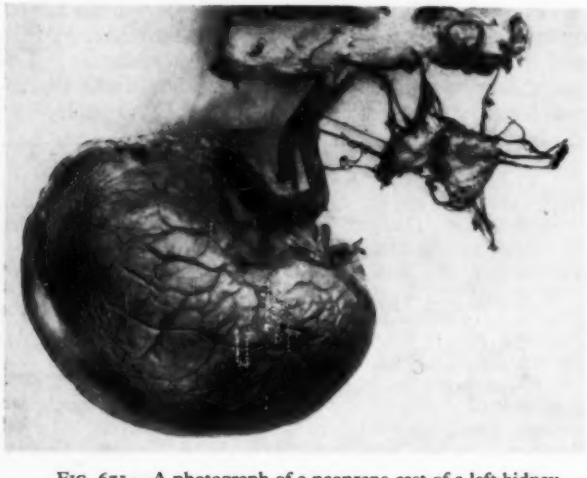


FIG. 671.—A photograph of a neoprene cast of a left kidney and adrenal gland of the dog. The circumferential source of the blood-supply to the adrenal gland is evident.

damage to part of the cortex and this seemed to offer a method of studying regeneration of the dog adrenal gland. The main difficulty in studying the true behaviour of the transplanted adrenal gland is largely one of surgical technique in being able to effect an immediate blood-supply to the gland. For the most part, implantation techniques in rodents have been used to study processes of adrenal regeneration. For this reason most of our ideas about adrenal regeneration are based exclusively on experiments involving rodent adrenal glands. Many rodent tissues possess remarkable powers of regeneration: a small portion of ovary, thyroid, or adrenal, for example, auto-implanted subcutaneously will survive, become revascularized, and regenerate. It is usual to qualify such a statement, as follows: provided there is a considerable insufficiency of that particular hormone. This is briefly what has come to be known as Halsted's law (1909), the validity of which will be discussed in the present paper.

So far as the rat thyroid gland is concerned, no hormonal insufficiency would appear to be necessary for its survival; by giving certain doses of thyroxine one can virtually eliminate any deficiency, and under such conditions auto-implanted thyroid tissue can survive and regenerate (Dempster and Doniach, 1955). This capacity of auto-implanted tissue to regenerate does not obtain, however, in larger mammals such as man and dog; Stone, Owings, and Gey (1934) reported constant failure of thyroid auto-implants in the dog. Accordingly, it is not profitable to employ implantation techniques in such species. In no species, on the other hand, are homo-implantation techniques likely to shed any further light on the problems of homografting. This generalization excludes, of course, experiments on pure strain rodents.

There are numerous reports in the literature on the remarkable effects following adrenal homo-implantation in humans: Hurst, Tanner, and Osman (1922); Currie (1924); Halpern and Arkuschenko (1927); Leschke (1928); Reinhart (1928); D'Abreu (1933); Beer and Oppenheimer (1934); Goldzieher and Barishaw (1937); Auslander (1938); Katz and Mainzer (1941); Thiersch (1943); and Broster and Gardiner-Hill (1946). Few serious observers feel inclined to attach any significance to these reports since no histological evidence of survival has ever been produced.

Levy and Blalock (1939) described a method of transplanting the dog adrenal so as to provide the gland with an immediate blood-supply. The kidney and its adjacent adrenal were removed in one block of tissue. The block of tissue was transferred to the neck, where the renal vessels were anastomosed to the carotido-jugular circulation. Under the conditions of this procedure the gland is partially supplied

by blood from branches arising from the renal artery (*Fig.* 671). By this technique Levy and Blalock (1939) successfully autotransplanted adrenal glands which maintained dogs in good health after the removal of the contralateral adrenal gland. This technique has not been sufficiently exploited by experimental surgeons, although it obviously offers many advantages over any other technique. Another technique for transplanting the dog adrenal gland has been described by Keeley, Dunphy, Quigley, and Bell (1940). An implantation technique has been described by Blodinger, Klebanoff, and Laurence (1926); this technique was quite unsuccessful.

The aims of this investigation are these :—

1. To demonstrate the behaviour of autotransplanted adrenal glands. Since the blood-supply to such adrenal glands is limited to those areas supplied by the branches from the renal artery and any area supplied by a capsular collateral circulation, it is mainly the zona glomerulosa which survives the insult of transplantation. This technique, it was thought, might afford a method of studying the mechanism of regeneration, if any exists, of the adrenal gland of the dog. Accordingly, comments will be made on the mode of regeneration of the adrenal gland of the dog in relation to the general theory of regeneration of the adrenal cortex.

2. To demonstrate the behaviour of homotransplanted adrenal glands. To demonstrate further that implantation techniques are not valid for studying the behaviour of tissues transferred from one animal to another of the same species. Accordingly, the behaviour of homotransplanted adrenal glands will be compared with that of homo-implanted adrenal glands of the dog and rat. The validity of Halsted's law (1909) will be considered in the light of these findings.

MATERIALS AND METHODS

Greyhound bitches of varying weights (22–25 kg.) were used. Rats of both sexes and of weight about 200–280 g. were used.

Technique of Transplanting the Kidney and Its Adrenal.—Via a transabdominal route, the left kidney and its adrenal were removed in one block of tissue and transferred to the neck. The renal vessels were sutured to the carotido-jugular vessels by an end-to-end technique described elsewhere (Dempster, 1953). The block of tissue was either transferred to the neck of the same dog (autotransplantation) or that of another dog (homotransplantation). In three instances the left kidney with its associated adrenal and ovary was transplanted to the left iliac vessels. This latter technique has been described elsewhere (Dempster, 1954; Dempster, Joekes, and Oeconomos, 1955), and all other associated techniques have been described elsewhere (Dempster, 1950, 1953).

In only one instance did the adrenal vein flow into the left renal vein. No attempt was made to anastomose the adrenal vein to any other vein in the neck as this, in any case, was not feasible. Bleeding from the adrenal vein can be quite substantial once the carotido-jugular circulation has been established in the kidney. Gentle compression on the adrenal vein has the effect of diverting the venous return through other small channels in the capsule of the adrenal gland and so into the renal vein. The blood in the adrenal vein clots, but this, fortunately, does not prejudice survival of the gland as a whole. Quick venous ligation does preclude survival.

A Note on Adrenalectomy in the Dog.—Rogoff and Stewart (1929) reported that unilateral adrenalectomy was a severe operation in cats. Britton (1930) in a review states, "It should be borne in mind that in the dog the operation is more difficult than in most laboratory animals".

In the present experiments, unilateral adrenalectomy associated with unilateral nephrectomy was not found to upset the dogs. The same procedure combined with autotransplantation of the block of tissue to the neck was very upsetting to the dogs in most instances. The usual clinical course was as follows: the dogs recovered slowly from the anæsthetic, refused food, and lay in an apathetic state for a few days: 6 dogs died 8–10 days after such a course and no apparent cause of death was established. This clinical course was unaltered by the administration of 15 mg. of cortisone per diem by mouth. Autotransplantation of the left kidney and adrenal to the iliac vessels was not upsetting to the dogs.

The only finding which might explain the systemic upset following adrenal transplantation was hæmorrhage into the adrenal as a result of infarction. No organisms were found in these necrosed adrenals. In a normal dog, tying the left adrenal vein results in sudden venous congestion of the gland and leads to a grave decline in the health of the dog, which in all respects resembles that seen in some instances following autotransplantation of the adrenal. Since in all cases the contralateral adrenal was intact, the systemic upset was not due to adrenal deficiency.

Implantation Techniques.—By implantation is meant the removal of an organ and its subsequent placing, in whole or in part, in another area of the body without an immediate blood-supply.

A. In the Dog.—

1. Unilateral adrenalectomy with immediate implantation of the whole adrenal to its former bed.

2. Unilateral adrenalectomy with immediate implantation within the spleen; usually the adrenal was cut up into thin slices prior to implantation.

B. In the Rat.—

1. Implantation of the whole or enucleated adrenal gland was made into the mesentery of the spleen. The implantation was associated with and without the removal of the contralateral adrenal.

Fixatives.—All adrenal glands were cut at various levels in their long axis and then fixed. The specimens were fixed in formol saline or in a modified Helly within five minutes of removal. Sections were cut at 5μ and, in certain instances, serial sections were made at various levels.

Stains.—The following were employed: H. and E., allochrome, methyl green pyronin orange G (Trevan and Sharrock, 1951), Sudan 3 and 4, Picro-Mallory, and reticulin.

The General Plan of the Experiment was as follows.—

1. *Experiments involving the Dog Adrenal Gland.*—

a. Auto-implantation of the adrenal gland was performed on 6 dogs (i) to the adrenal bed, and (ii) within the spleen. After 30 days the dogs were

sacrificed and the auto-implants were removed for histological examination.

b. Homo-implantation of the adrenal gland was performed on 6 unilaterally adrenalectomized dogs. The site used was the adrenal bed. After 30 days the dogs were sacrificed and the homo-implants were removed for histological examination.

c. Auto-transplantation of the left kidney and adrenal (and in some instances the left ovary as well) to the neck was effected in 22 dogs. (The technique

FIG. 672.—A photomicrograph of sections of rat adrenal glands. Unilateral adrenal enucleation was carried out and after an interval of thirty days the above specimens were removed. The normal adrenal gland has hypertrophied and the enucleated adrenal gland has regenerated a new cortex. Debris is evident in the centre of the latter. H. and E. (× 9·3.)

has been described elsewhere (Dempster, 1950).) In 3 dogs the left kidney, adrenal, and ovary were auto-transplanted to the iliac vessels; the technique of this procedure has been described (Dempster, 1954, c; Dempster, Joekes, and Oeconomos, 1955). In 5 instances, two weeks after the operation, the contralateral adrenal and kidney were removed. At varying intervals after the second procedure, the dogs were sacrificed and the transplanted organs removed and fixed for histological examination. The dogs were maintained on a high-salt diet for four days following the second operation, after which they were maintained on normal quantities of salt (3 g. per day). When the dogs were sacrificed, the adrenal sites were inspected for regenerated adrenal remnants.

d. Homotransplantation of the adrenal and kidney (and in some instances, the left ovary as well) was effected in 9 dogs. The host, in all instances, retained its own adrenal glands intact but was unilaterally nephrectomized. When the homotransplanted kidney became anuric the block of tissue containing kidney, adrenal, and ovary was removed for histological examination.

e. In 3 dogs unilateral adrenalectomy was performed. Ten weeks later they were sacrificed and the remaining adrenal was removed, weighed, and fixed for histological examination.

2. *Experiments involving the Rat Adrenal Gland.*—

a. Bilateral adrenalectomy with simultaneous auto-implantation of one adrenal gland was performed on 6 rats. The auto-implants were removed at intervals varying from 8–30 days later.

b. Bilateral adrenalectomy with simultaneous homo-implantation of one enucleated adrenal was performed on 9 rats. At intervals varying from 8 to 30 days later the homo-implants were removed.

c. Unilateral enucleation of the adrenal was performed on 14 rats: the contralateral adrenal was retained. The animals were sacrificed 30 days later, when the specimens were removed, weighed, and examined histologically.

d. In 6 rats enucleation of both adrenal glands was performed. The enucleated material and the remaining capsule were then placed in fixative. In this way one could determine what actually is left behind within the capsule after enucleation.

e. Bilateral enucleation of the adrenals was performed in 6 rats. The rats were sacrificed 30 days later, when the specimens were removed, weighed, and examined histologically.

Weights of Normal and Transplant Adrenal Glands.—A series of 10 dogs (weights 22–25 kg.) provided the normal range of adrenal weights. All transplanted adrenals were weighed on removal. The adrenal glands from 10 rats (weights 250–280 g.) were removed and weighed. The average weight corresponded closely to the theoretical weight on the basis of the adrenal weight being 0·02 per cent body weight (Grollman, 1936).

Assessment of the Area of Supply to the Left Adrenal Gland of Blood from the Left Renal Artery Branches.—Blocks of tissue containing left kidney and adrenal were removed from 10 normal dogs. Indian ink was immediately injected via the renal artery. After the injection, the adrenal glands were cut in their long axis and the area of ink present was noted.

RESULTS

1. Weights of Normal and Transplanted Adrenal Glands.—In a series of 10 normal adrenal glands examined, the following measurements were obtained:—

Right adrenal: average weight 2·9 g. (range 1·7–3·9 g.); Left adrenal: average weight 3 g. (range 1·9–3·5 g.).

The average weight of the autotransplanted adrenal glands was 4·5 g. This increase in weight was largely due to a marked œdema in the peri-adrenal tissues similar to that observed in the perirenal tissues following transplantation of the kidney (Dempster, 1954, a). Thus, the weight of the autotransplanted adrenal gland was of little significance so far as assessing the extent of hypertrophy was concerned.

The weights of the three right adrenal glands removed from dogs unilaterally adrenalectomized three months previously, fell within the average range of normality, which was surprising in view of previous reports (Baker, 1937).

2. Weights of Rat Adrenal Glands following Enucleation.—Ten out of 14 rats which were subjected to unilateral adrenal enucleation showed signs of regeneration of the enucleated adrenal as well as hypertrophy of the contralateral adrenal. Since part of the weight of the enucleated adrenal gland is made up of debris (*Fig.* 672), it follows that one is not able to assess accurately the weight of regenerated enucleated adrenals. One can say, however, that the weight of the contralateral adrenal

gland never reached the theoretical weight of adrenal glands for the individual rats (theoretical weight 0·02 per cent body-weight—Grollman, 1936).

3. Enucleated Material and Enucleated Capsule Remnants of the Rat Adrenal Gland.—In all instances the enucleated material consisted of zona fasiculata and reticularis and the medulla. The tissue remaining within the capsule consisted of zona glomerulosa and occasionally a portion of zona fasciculata which serves as a reminder that enucleation is seldom complete.

4. The Area of the Left Adrenal Gland of the Dog supplied by Branches of the Left Renal Artery.—Since there is a rich collateral circulation in the zona glomerulosa, one would expect that if blood reaches the capsule, a wide area of the zona glomerulosa would become filled with blood from any of its main sources. Indian ink injected via the renal artery should, on the above basis, show a wide distribution in the zona glomerulosa. This was not always the case. Following indian ink injection via the left renal artery, no ink was detected in 3 out of 10 of the adrenal glands. In one instance the adrenal gland was completely filled with ink. In the remaining six adrenal glands ink was found in scattered segments only. This method of assessing the area of blood supplied by the renal artery branches is open to criticism as it leaves out of account the extent to which the collateral circulation can open up following transplantation. However, in spite of this limitation, this technique does provide a rough assessment of the number of failures one might expect in transplanting the left adrenal gland and its adjacent kidney. The above results were interpreted to mean that in 3 out of 10 no renal artery branches to the adrenal gland were present, in 1 out of 10 numerous branches were present, and in 6 out of 10 a variable number were present. In the homotransplant series 2 out of 9 were failures since both adrenal glands were completely necrosed. In the autotransplant series 3 out of 25 were complete failures, and in 1 out of 25 (95 days' survival) the blood-supply to the adrenal gland was virtually complete as only one small segment showed necrosed tissue (*see Fig.* 675). In 21 out of 25 autotransplants, surviving areas were observed in both cortex and medulla; usually the zone best preserved was the zona glomerulosa. It is not implied that the surviving areas were the result of regeneration; those areas survived because their blood-supply was adequate. The autotransplanted adrenal gland, therefore, provided a technique for the study of adrenal regeneration with particular reference to whether centripetal migration of glomerulosa cells can occur. No such evidence emerged.

5. The Nature of the Blood-supply to the Adrenal Gland.—

Dog.—The arterial supply to the adrenal gland approaches it from all directions, and over its capsule there is a rich collateral circulation. The blood-flow courses from the capsule to the medulla and the venous blood flows into one main vein. The key structure in the adrenal gland, from the vascular point of view, is the capsule. Adrenal implantation has been attempted in the past by surgeons without an adequate awareness of the significance of the capsule. The capsule is of vital importance in the regeneration of the adrenal gland. With these facts in mind, there would appear to be no rationale for the technique employed by Broster and Gardiner-Hill (1946) in which the alleged arterial supply to the adrenal gland (i.e., the inferior epigastric artery) was inserted into the adrenal vein. The arterial supply to the dog adrenal has been well described by Flint (1900). The cortex of the adrenal is well supplied by a network of anastomosing capillary plexuses.

According to Flint (1900) the adrenal is supplied by three types of vessels: (1) that which supplies the glomerulosa and forms a collateral circulation; (2) that which supplies the fasciculata and reticularis; and (3) that which supplies medulla direct. The latter two types of vessels are end-arteries. The richest supply of vessels is to the glomerulosa region from which small veins arise and emerge on the capsule surface. This explains, in part, why the zona glomerulosa is usually the area least damaged by transplantation.

6. A Note on the Histological Features of the Adrenal Gland.—

Rat.—The adrenal cortex consists of the usual three zones: glomerulosa, fasciculata, and reticularis. The glomerulosa consists of single rows of glomerular loops. The reticular zone consists of wide capillary meshes which are larger in proportion to the amount of parenchyma; passive congestion could, theoretically, be easily produced. No islets of glomerulosa cells were observed in the capsule.

Dog.—The zona glomerulosa is well developed and consists of large double arches which are convex outwards. Small islets of glomerulosa cells can often be seen in the capsule: these islets were observed in 70 per cent of the normal adrenals examined. When they did occur, they were small and usually not more than two or three in the whole circumference of the capsule.

Nicander (1952) found also that there were few of these islets in the capsule of the dog adrenal. For any assessment of glomerulosa-cell proliferation in autotransplanted adrenal glands this latter fact must be kept in mind. Before reaching any conclusion about the possibility of islet-cell proliferation in an autotransplanted adrenal, one should always consult the histology of the contralateral normal adrenal.

The zona reticularis is a well-defined zone. There is no evidence of cellular breakdown, debris, or any signs of degeneration.

Occasionally, just beneath the capsule and between the glomerulosa loops, there may be small aggregations of mature plasma cells. In assessing the significance of these cells, the contralateral adrenal should be examined; it occasionally happens that the normal adrenal gland is the seat of mature plasma-cell aggregations. In normal glands, these plasma cells are always confined to the capsule and zona glomerulosa. This fact is important in assessing the significance of the immature plasma-cell infiltration which occurs in homotransplanted adrenal glands.

In normal adrenal glands (rat, dog, cat, and human) no observation was made which could support the notion that the zona reticularis is a zone in which cells are being destroyed. It may not be too strong a claim, in view of similar evidence from

other workers, that this former misconception be abandoned. In a recent study Chester Jones and Wright (1954) state, " Dying cells, as judged by the usual criteria, are not numerous in the zona reticularis but some normally can be seen. . . ." Further on these authors conjecture " It is probable that the whole process of cell change is a slow one " (1954). One might ask if there are any dying cells to be seen in the zona reticularis of the regenerating enucleated rat adrenal where one might expect a quicker turnover of cells; the present experiments would definitely deny this. It must be admitted that the centripetal migration theory is lacking in any quantitative measurement.

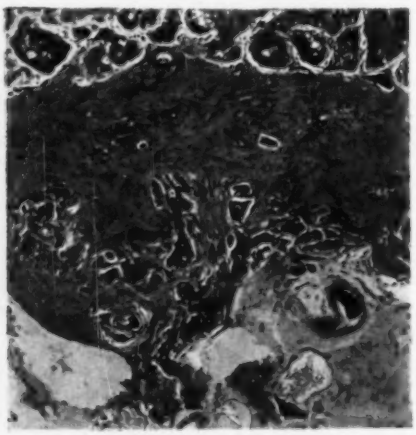


FIG. 673.—A photomicrograph of a section of an autotransplanted adrenal (dog). Nodules of glomerulosa-like cells can be seen in a thickened capsule. Indian ink was injected via the renal artery and can be seen filling vessels in the adrenal capsule. H. and E. (× 100.)

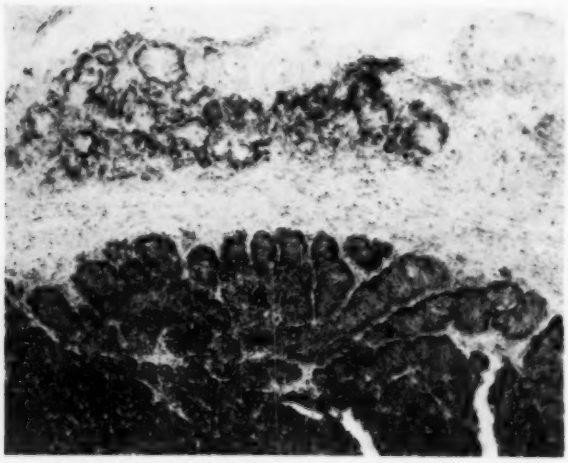


FIG. 674.—A photomicrograph of a section of an autotransplanted gland (dog). Cholesterol can be demonstrated in the glomerulosa-like cells in the capsule. Sudan 3 and 4. (× 65.)

7. Histological Features of the Autotransplanted Adrenal.—

Dog.—The sectioned adrenals presented areas of living and dead parenchyma. The surviving parenchyma might consist of all three zones of the cortex and the medulla (21 out of 26); the area most consistently preserved was the zona glomerulosa (23 out of 25).

The dead areas contained hæmorrhage, necrosed cells, pyknotic nuclei, and a polymorph infiltration mainly confined to the zona glomerulosa. Rigdon and Swann (1953) have described coagulative necrosis and a polymorph infiltration in the dog adrenal following a period of anoxia.

From no area of surviving zona glomerulosa overlying a zone of necrosis were any signs observed of glomerulosa cells undergoing centripetal migration.

The capsule of the adrenal was usually thickened. Within the thickened capsule, a marked increase in cell content was obvious; these cells consisted mainly of fibroblasts. In the capsule of all those adrenals removed over seven days following transplantation, nodules of glomerulosa-like cells were a striking feature (*Fig.* 673). These nodules were often widely separated from the zona glomerulosa and occasionally were to be seen over an area of necrosed zona glomerulosa. It is unlikely, therefore, that these nodules represent cells from the zona glomerulosa which have grown outwards.

These nodules were usually intimately related to large blood-vessels. They contained cholesterol (*Fig.* 674). There was no indication that the cells in the nodules differentiated into cells resembling those of the zona fasciculata and zona reticularis or that they showed any tendency to grow into the zona glomerulosa. There did seem a tendency to grow laterally within the capsule.

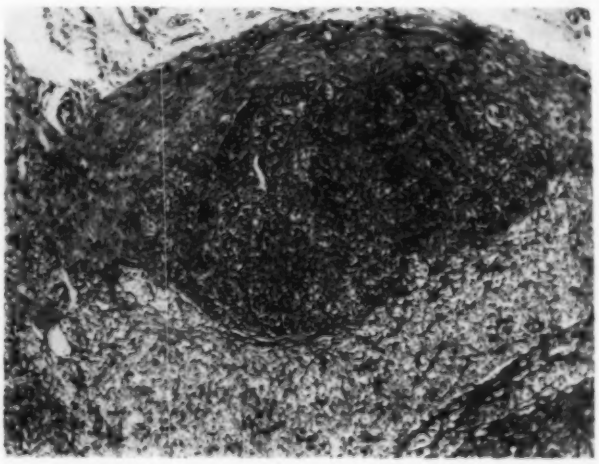


FIG. 675.—A photomicrograph of a section of an autotransplanted adrenal gland after 95 days (dog). An area comprising outer fasciculata and reticularis is necrosed as a result of the operation. No effort was made to repair the defect by cells growing inwards. The thickened capsule is evident. H. and E. (× 46·5.)

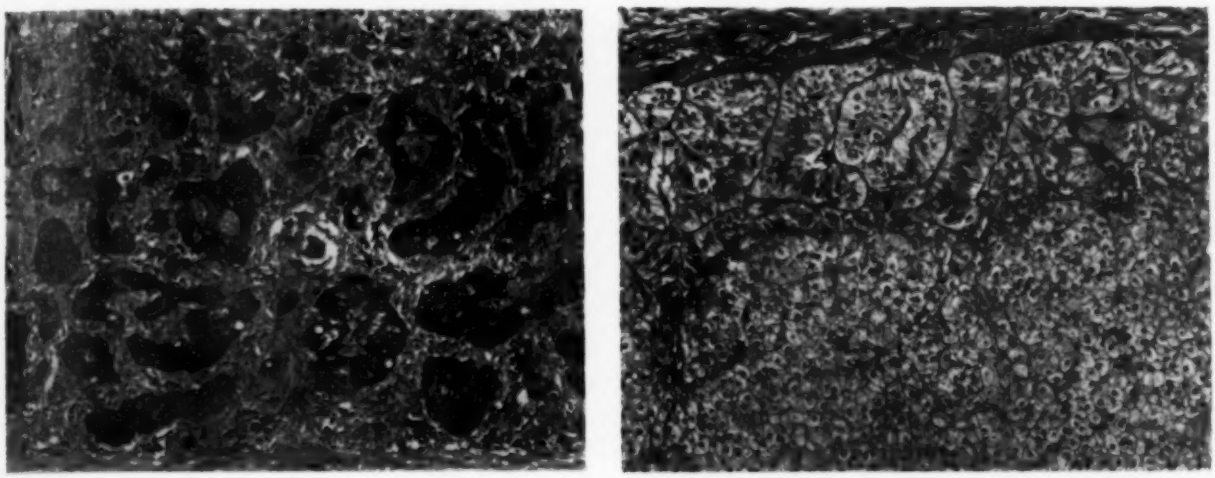
In the autotransplanted adrenal gland, which was removed after 95 days, nodules of glomerulosa-like cells in the capsule were not a feature. Virtually the whole gland was preserved intact. The one necrosed area involved zona fasciculata and reticularis, the debris of which were clearly seen and which had been partially phagocytosed (*Fig.* 675). The overlying zona fasciculata and glomerulosa cells did not move inwards to replace the dead cells in the zona reticularis.

Histology of the Homotransplanted Adrenal Gland.—Nine adrenal glands were homotransplanted with their adjacent kidneys; in some cases the ovary was

included as well. The block of tissue was removed when the kidney became anuric following a period of good secretion; anuria in this context has been explained elsewhere (Dempster, 1954, b). Two of the adrenal glands were failures because of inadequate blood-supply from the renal artery.

In the remainder, removed at intervals ranging from 4 to 10 days, areas of living and dead parenchyma were seen. The zona glomerulosa, although obviously alive, showed a curious pattern (*Fig.* 676 A) which is far removed from the normal (*Fig.* 676 B). There was a widespread immature plasma-cell infiltration in all zones of the adrenal gland (*Fig.* 677); this infiltration exactly resembled that already seen in the homotransplanted kidney (Dempster, 1953); a similar cellular infiltration was found in the homotransplanted ovary (*Fig.* 678). The capsule of the homotransplanted adrenal gland was thickened and contained immature plasma cells and pyronin-positive fibroblasts.

Histology of the Auto-implanted and Enucleated Adrenal Glands of the Rat.—At the end of seven days, rows of cortical cells can be seen in the enucleated adrenal gland. These cells seem to migrate inwards quite undeterred by the central mass of fibrin and other cellular debris (*Fig.* 679). In the autotransplanted adrenal gland of the dog, it will be remembered, no invasion of the underlying dead zones was found; one was unable to rule out the part played by the dead zone in preventing an inward migration of cells. There is no doubt, however, that in the rat, in spite of a central debris, centripetal migration of glomerulosa cells occurs. There was no indication that the regenerating cells originated in the fibroblasts of the capsule—as reported by Salmon and Zwemer (1941). A recent report by Brenner, Patt, and Wyman (1953) has described the changes in the auto-implanted rat adrenal and the present work has nothing to add. The main mass of the auto-implant dies. Within a few days, the subcapsular cells start



A B

FIG. 676.—A, Photomicrograph of a section of a homotransplanted adrenal gland (dog). There is widespread disorganization of the adrenal cortex. There is an immature plasma-cell infiltration extending inwards to the zona reticularis. Methyl green pyronin orange G. (× 170.) B, Photomicrograph of a section from a normal adrenal gland of the dog. H. and E. (× 105.)

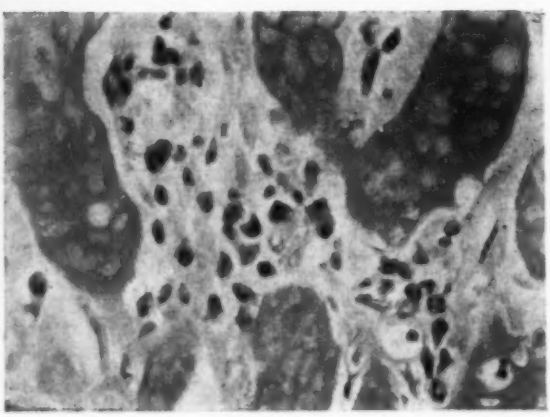


FIG. 677.—Photomicrograph of a section of a homotransplanted adrenal gland (dog). This is an enlarged view of an area in the field shown in *Fig.* 676 A. The immature plasma cells are evident. Methyl green pyronin orange G. (× 432.)

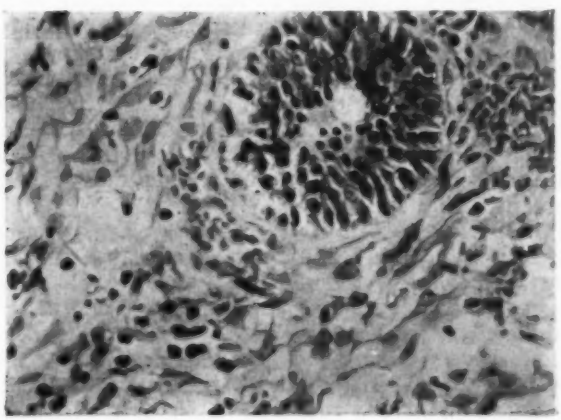


FIG. 678.—Photomicrograph of a section of a homotransplanted ovary (dog). The general structure of the ovary is retained, but immature plasma cells are evident. Methyl green pyronin orange G. (× 400.)

to regenerate and move inwards to constitute a new cortex, as occurs in the enucleated adrenal gland of the rat. It has been reported that by the seventh day after auto-implantation, there is considerable adrenal cortical activity (Komrad and Wyman, 1951). Implantation into liver and spleen gives equally good results in rats (Butcher, 1948).

8. Local Cellular Reaction.—

1. *Around Implanted Adrenals.*—In the dog a cellular reaction developed around both auto- and homo-implanted adrenals: the adrenals in both instances were completely necrotic. Crowe and Wislocki (1914) had similar experiences with implants of dog adrenal. The cellular reaction consisted predominantly of polymorphs, but also included pyronin-positive fibroblasts and plasma cells. The cellular reaction was mild in the case of auto-implanted adrenals, but was very intense around homo-implanted adrenals.

FIG. 679.—Photomicrograph of a section of a rat adrenal gland seven days after enucleation. Cords of cells can be seen growing inwards from the subcapsular region. H. and E. (× 125.)

In the rat no cellular reaction developed around the regenerated auto-implanted adrenals. A cellular reaction consisting mainly of polymorphs and some plasma cells developed around necrosed homo-implanted adrenals.

2. *Around Transplants* (*Dog*).—No cellular reaction developed in the host tissues immediately adjoining the transplants. The capsule in the case of homotransplanted adrenals was involved in an immature plasma-cell infiltration identical to that described in the renal capsule (Dempster, 1953).

DISCUSSION

The Mode of Regeneration of the Adrenal Cortex.—Most of the present notions about the mode of regeneration of the adrenal cortex have been built up almost exclusively on those exemplified by the rat. Hoerr (1931), using the rat adrenal, confirmed Gottschau's (1883) concept of the continual evolution of the adrenal cortical cells from the region beneath the capsule. From the periphery, young cells pass through various phases and reach maturity in the zona reticularis; there they become effete and are removed by macrophages. So far as the dog adrenal cortex is concerned, there is not the slightest suggestion that a similar process is at work. Hoerr (1931) showed that the regeneration of a damaged adrenal cortex was brought about by mitotic division of any surviving parenchymal and interstitial cells in the subcapsular region. In the rat it is usually alleged that only the cells of the zona glomerulosa show mitotic figures, whereas mainly degenerate cells are to be found in the zona reticularis.

Zwemer (1936) confirmed, in the rat, the findings of Hoerr (1931), but put forward the notion that the cells of the zona glomerulosa arose from cells in the capsule resembling connective-tissue cells. Ingle and Higgins (1938) found no evidence of fibroblasts in the adrenal capsule. Bennett (1940), studying the cat adrenal gland from a histochemical point of view, was inclined to agree with the migratory theory, although his facts were clearly not in its favour.

Salmon and Zwemer (1941) claimed that, by intravitam staining with trypan blue, the origin of the cortical cells from the capsule could be demonstrated. Calma and Foster (1943) were unable to confirm the claim of Salmon and Zwemer (1941) and were of the opinion that certain cells in the inner part of the adrenal capsule, by mitotic division, develop into cells characteristic of the zona glomerulosa. Baxter (1946) categorically rejected the claim of Salmon and Zwemer (1941) and pointed out the many shortcomings of the experiments of these workers. Salmon and Zwemer (1941), for example, claimed that the effete cells of the zona reticularis stained diffusely with trypan blue intravitam: Baxter (1946) considered such cells to behave like macrophages and produced evidence suggesting that the number of these cells in the zona reticularis was an index of the amount of cell destruction in the adrenal gland.

Tonutti (1941, 1942, a, b) was the first to raise a voice of protest against the migratory theory. His concept, however, of the behaviour of the cortical cells is equally bizarre. It is his opinion that the cells of the zona glomerulosa and the zona reticularis are areas containing cells in an inactive state; both areas can transform their cells into active fasciculata cells on demand.

Whitehead (1943) continued the protest against the notion of centripetal migration; using guinea-pigs, he found no evidence that mature cortical cells moved either outwards or inwards. There was no sign of cell breakdown in animals under six months. Mitosis was most noticeable in young animals; this means that mitotic activity is greatest when no cells require replacing.

Gineste (1946), using rats injected with colchicine and other drugs, found the greatest amount of mitosis in the outer third of the zona fasciculata. Therefore, he argued that the source of the reticularis cells could not be in the zona glomerulosa but rather in the zona fasciculata; this attitude is echoed later by Chester Jones and Wright (1954).

Deane and Greep (1946), using rats, found that the atrophic changes following hypophysectomy affected mainly the zonæ fasciculata and reticularis; the zona glomerulosa was unaffected. Under these conditions there was no evidence that glomerulosa cells migrated inwards. This evidence is not altogether satisfactory. Hypophysectomy completely changes an animal; in fact, it is a new animal with

entirely different metabolic needs. To draw general conclusions about the regenerative processes of the adrenal gland from the behaviour of the cells in hypophysectomized animals would not appear to be justified; a hypophysectomized animal has obviously no need for zona fasciculata and reticularis.

The Relation of the Adrenal Cortex to the Anterior Pituitary.—Tepperman, Engel, and Long (1943) reported that hypophysectomy caused atrophy of the zona fasciculata and zona reticularis of the rat adrenal. Earle, de Bodo, Schwartz, Farber, Kurtz, and Greenberg (1951) noted atrophic changes in all zones of the cortex of the dog adrenal; such dogs could withstand sodium restriction but could not respond normally to a water load.

Some interest has centred around the fact that hypophysectomy causes little structural change in the zona glomerulosa. Swann (1940) and Deane and Greep (1946) and Greep and Deane (1947; 1949, a, b) and Yoffey and Baxter (1949) have suggested that the zona glomerulosa is independent of the anterior pituitary. Cater and Stack-Dunne (1953) have found decreased mitoses in the zona glomerulosa in hypophysectomized rats. Hypophysectomy causes no upset in electrolyte balance but does cause some carbohydrate metabolic deficiency. This has led to some speculation, by the above authors, about the possible existence of 'salt' and 'carbohydrate' hormones. Chester Jones and Wright (1954) have opposed the notion that the zona glomerulosa produces a 'salt' hormone; they suggest that it is the zona fasciculata which manufactures this hormone. Greep and Deane (1949, a) put forward the notion that the age of the adrenal cell determined the nature of its cell product. They suggested that the cells of the zona glomerulosa controlled salt and water metabolism; Bergner and Deane (1948) suggested that the cells of the zona fasciculata controlled protein and carbohydrate metabolism. Ingle (1951) has marshalled a considerable amount of evidence against the notion of the autonomy of the zona glomerulosa. Other evidence in support of Ingle is to be found in the papers of Smith (1930), Chester Jones (1949), Lane (1951), Baker (1952), and Selye and and Stone (1950). Brownell, Hartman, and Reiman (1950) found that after enucleating the rat adrenal gland, a new cortex reformed but the serum-sodium remained low, and they suggested that this insufficiency was not due to the zona glomerulosa alone.

Simpson, Evans, and Li (1943) confirmed the findings of Tepperman and others (1943), but also reported that the cortex could be restored to normal by the administration of adrenocorticotrophin. Cortisone can cause atrophy of the adrenal cortex. Winter, Hollings, and Stebbins (1953) sought a method of overcoming this side-effect of cortisone. They found that methyl androstenediol administered with cortisone prevented the atrophic effect of the latter.

Hypertrophy of the remaining adrenal gland after unilateral adrenalectomy has been assumed to be under the control of the anterior pituitary. Ganong and Hume (1954) have shown that hypertrophy can be abolished if hypothalamic lesions involving at least one-half of the median eminence are induced. This complicates the evidence that maximal adrenal stimulation in the human is dependent on continuous infusion of low concentrations of ACTH; this has also been confirmed by *in vitro* studies of perfused bovine adrenal glands (Macchi and Hechter, 1954). Crooke and Gilmour (1938) noted cellular degeneration of rat adrenal glands four days after hypophysectomy. Cater and Stack-Dunne (1953) have indicated that pituitary extracts given to hypophysectomized rats cause increased mitosis in the zones where mitotic activity usually occurs.

Thus, there is a great deal of evidence to support the notion that the size and the secretory activity of the adrenal cortex are controlled by ACTH. Ingle (1951) has reviewed the relationship in some detail. Without ACTH, the adrenal cortex has a very limited function.

Mitchell (1948) has described two zones of high mitotic activity: (1) the glomerulosa; and (2) the outer layer of the zona fasciculata. Lying between these two layers is a zone which is mitotically inert. It was his opinion that, in the rat, capsular cells do not contribute to any extent to the cortex after the first two weeks of post-natal life.

Yoffey and Baxter (1947) have reported functionally significant changes in the zona reticularis, and this evidence is at variance with the classical centripetal migration theory.

On data collected from a comparative anatomical survey, Nicander (1952) found no evidence of centripetal migration in any species. His comparative anatomical study produced data conflicting with what has often been held to be established fact:—

1. In the bovine adrenal cortex there were no apparent signs of degeneration in the cells of the inner cortex.

2. Pigment in the cortical cells has often been interpreted as a sign of degeneration. Nicander points out that pigment can be found in the zona glomerulosa of many species.

Nicander summed up his evidence thus: ". . . it seems that no real migration of cells takes place within the adrenal cortex".

Lever, Cater, and Stack-Dunne (1953) have found no evidence that the zona intermedia (i.e., a thin zone between the zona glomerulosa and the zona fasciculata) was an area of active mitosis.

Baker and Bailiff (1939) traced the regenerative process in the rat adrenal by enucleating the gland in situ. Following this procedure, narrow cords of cells grow from the capsular region and form groups of cells which later form the zona glomerulosa. This regenerative process is most active in the first few days and is complete in under thirty days. The findings of Baker and Bailiff (1939) were confirmed by Greep and Deane (1949, a), who went further and claimed that the regenerated adrenal secreted hormones governing both salt and carbohydrate metabolism and that functional zonation was effected; they found no evidence of fibroblasts being transformed into cortical cells. A somewhat novel attitude to the centripetal migratory theory is that of Chester Jones and Wright (1954). They suggest that the zona glomerulosa is a 'vegetative backwater' of cortical cells and but for mechanical barriers, such as the medulla, there might be no zonation whatever, as is the case in fish and some reptiles.

Ingle (1951) claimed that the enucleated adrenal gland of the rat would not regenerate unless the

contralateral adrenal gland was removed. The present experimental evidence does not support this. It is difficult to account for the discrepancy in the results. One requires to dissect carefully in the perirenal fascia in order to find regenerated enucleated adrenal glands in cases where the contralateral gland remains intact.

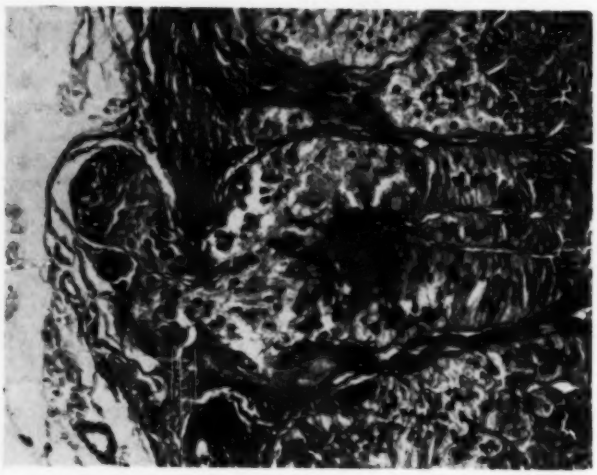


FIG. 680.– Photomicrograph of a section of a normal adrenal gland (rat). An area of zona glomerulosa can be seen projecting through a gap in the capsule. H. and E. (× 170.)

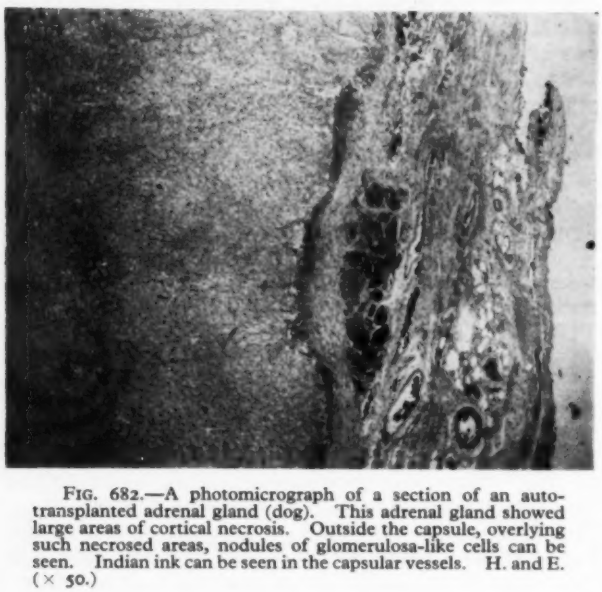


FIG. 682.—A photomicrograph of a section of an auto-transplanted adrenal gland (dog). This adrenal gland showed large areas of cortical necrosis. Outside the capsule, overlying such necrosed areas, nodules of glomerulosa-like cells can be seen. Indian ink can be seen in the capsular vessels. H. and E. (× 50.)

The present experiments confirm fully that the enucleated rat adrenal can regenerate a new cortex; the medulla does not regenerate. The histological examination of enucleated material confirmed that usually all the cortex except the zona glomerulosa was removed. At the end of thirty days the cortex had completely regenerated itself, along with a normal vascular pattern. There can be no doubt that the cells of the fasciculata and reticularis, in this experiment, arose from the glomerulosa.

Gruenwald and Konikov (1944), in a comparative survey of the mammalian adrenal, suggested a new method whereby adrenal cortical cells might be replaced from the capsule. They suggested that complete new cells become incorporated as a layer into the outer cortex (*Fig.* 680). There appeared no doubt in their minds that the new cells were moving

FIG. 681.— Photomicrograph of a section of a normal adrenal gland (dog). An area of zona glomerulosa can be seen projecting through a gap in the capsule. H. and E. (× 275.)

inwards. A similar feature can be seen in the dog adrenal (*Fig.* 681). But these groups of cells, on the contrary, may be moving outwards. The group of cells may be merely a herniation through a weak area of the capsule and of no further significance. This is obviously a debatable point. There is no evidence to justify the assumptions of Gruenwald and Konikov (1944). These authors also suggested that a moderate demand on the adrenal gland resulted in mitotic activity in the outer layer of the fasciculata; if such a demand increased, glomerulosa cells, they suggested, migrated inwards without showing signs of mitosis. They pointed out that cells in mitosis are unable to function normally. If, however, the adrenal contains a large zona glomerulosa, as in the dog, the reserve of cortical cells is not so frequently exhausted. There is some evidence in the present experiments that this latter suggestion may be correct in the case of the dog since the zona glomerulosa did not vary significantly after unilateral adrenalectomy.

Regeneration of the Transplanted Adrenal of the Dog.—In the present experiments no evidence of centripetal migration was found. There was some evidence that glomerulosa cells developed and hypertrophied in the capsule to form numerous islets. The new glomerulosa-like cells which arise in or grow into the capsule of the transplanted adrenal show no signs of differentiating into fasciculata-like cells. As to whether such islets migrated inwards or outwards was not determined as the evidence was conflicting. However, the first problem to be settled is the cell of origin of these new islets of glomerulosa cells. The possibilities to be considered are these :—

1. *The Zona Glomerulosa* : This would imply that the islets of glomerulosa cells grow outwards from the zona glomerulosa into the capsule. It might be conjectured that such cells are growing into an area

rich in blood-supply. Against this possibility is the fact that islets of cells can be seen in the capsule overlying areas of complete necrosis (*Fig.* 682).

2. *Capsule Cells*: There is no doubt that the capsule of the transplanted adrenal becomes more cellular and more dense after the operative procedure. From what cells could these extra-zonal glomerulosa-like cells arise? It has already been pointed out that Zwemer (1936) considered that glomerulosa cells arose from fibroblasts in the capsule of the rodent adrenal. Cater and Stack-Dunne (1953) found some mitotic figures in the capsule of normal rats. In the dog adrenal, occasional glomerulosa-cell islets have been found in the capsule. It is possible, therefore, that the glomerulosa-like cells arise from fibroblasts in the capsule. However, these islets in the auto-transplanted adrenal gland do not necessarily indicate a process of regeneration.

The next problem to settle is the direction of movements of these aggregations of glomerulosa-like cells. There was no evidence of their growing into the zona glomerulosa. They seemed to spread laterally in the capsule itself and were always intimately associated with a rich blood-supply. In spite of marked aggregations of these cells, no further differentiation into cells of zona fasciculata and reticularis was observed.

The Centripetal Migration of Adrenal Cortical Cells.—It is a fact that the enucleated rat adrenal can reconstitute its cortex within thirty days. This implies that glomerulosa cells have differentiated into cells of the inner two zones. In the present experiments on the dog no evidence of centripetal migration was observed. Yoffey (1952) has voiced the opinion that it is "unfortunate that so much attention has been devoted to the rat". In the same article Yoffey has suggested that only in small adrenal glands would the migratory theory be at all plausible. From a comparative anatomical and physiological point of view, it may be difficult to accept this suggestion. It would imply that similar cells in different animals possess a different functional significance. From comparative anatomical studies, Bourne (1949) concluded: "Finally, the most interesting fact which emerges from this work is not the differences in structure which are present in the adrenals of the members of the various mammalian orders, but their remarkable constancy."

However, physiological differences may and do exist. Yoffey (1955) has shown that in relation to the alkaline phosphatase reaction there is a complete reversal of zoning as between the rat and guinea-pig on the one hand and man on the other. Nelson and Woodard (1949) found that in dogs D.D.D., by mouth, caused atrophy of the zona fasciculata and reticularis. Sheehan, Summers, and Nichols (1953) showed that no such effect occurred in humans in spite of obvious accumulation of D.D.D. in these zones. It is perhaps unwise to argue that zones which occupy similar anatomical positions in various mammals necessarily have the same function.

It seems impossible to reconcile the various findings in dogs on the one hand and rats on the other with a unified theory of adrenal regeneration. It is clear, however, that in the dog no centripetal migration occurs. A valid criticism would be that the dead zones impeded any centripetal migration of cells. In the rat, centripetal migration is clearly indicated only in the regenerating enucleated adrenal gland. Whether this occurs normally has still to be proved. So far as adrenal regeneration in man is concerned, a study of the mode of regeneration of adrenal remnants following bilateral adrenalectomy might throw some light on the subject.

Adrenal Implantation.—The sites used by previous workers have included the following: spleen, rectus sheath, subcutaneous tissues, deep peritoneum, omentum, ovary, cerebral cortex, and anterior chamber of the eye.

The removal of the rat adrenal gland and its successful auto-implantation in another site has been reported by many workers. Turner (1939) auto-implanted rat adrenal glands to the anterior chamber of the eye in guinea-pigs. He found that a higher percentage persisted in bilaterally adrenalectomized animals. This appeared to him to be in conformity with Halsted's law (1909); on the other hand, he did find that survival of homo-implants occurred even when the host had both adrenals intact. Turner (1939) drew attention to the fact that it was the anterior pituitary hormone which controlled the regeneration of the auto-implanted adrenal. Dunphy and Keeley (1940) auto-implanted rat adrenals into the ovaries and reported viable grafts. Bernstein (1950) reported that adrenal auto-implants survived in the spleen and mesentery of bilaterally adrenalectomized rats; he concluded, from his results, that the liver plays no essential role in the metabolism of the adrenal cortical steroids. Ingle (1951) found that an enucleated adrenal gland did not regenerate in the presence of an intact adrenal gland; he also concluded that this was in accordance with Halsted's law. Darcy (1952) reported survival for some months of thin slices of adrenal glands homo-implanted subcutaneously in rabbits. Successful growth occurred in both normal and unilaterally and bilaterally adrenalectomized rabbits. This finding would appear to conflict not only with Halsted's law but also with what is generally known about the fate of most homo-implanted tissues. Pomerat, Breckenridge, and Gordon (1944) showed that adrenal homo-implants from newborn rats could survive, differentiate, and function in the cerebral cortex of adult adrenalectomized rats. In the present experiments no information was obtained about the behaviour of homo-implanted adrenals except that they were not successful. Using a vascularized chamber technique, Williams (1953) found that implants of zona glomerulosa could form cells resembling those of zona fasciculata in adrenal deficient rabbits.

Rogoff and Stewart (1927, 1928) found that in dogs the adrenal gland resisted secondary vascularization after auto-implantation. They reported, also, that pregnancy prolonged the survival of all bilaterally adrenalectomized dogs; the same feature was observed during 'heat'. The resistance to revascularization was borne out in the present experiments. It must be stressed, therefore, that auto-implantation of the adrenal is not a valid technique for studying the behaviour of an adrenal gland transferred to another site in the body of larger mammals.

A Possible Sequence of Events following Unilateral Enucleation of the Rat Adrenal Gland.—The finding that 10 out of 14 unilaterally enucleated adrenals regenerated is at variance with previous reports. It is, of course, easy to overlook the regenerated enucleated adrenal as it is covered with perirenal fat and scar tissue. In this context the alleged hypertrophy of possible supernumerary adrenal tissue was not encountered. Both normal and enucleated adrenals showed changes ; the former hypertrophied and the latter regenerated (*Fig.* 672). It is possible that delicacy in handling the vascular supply to the left adrenal of the rat determines whether or not regeneration occurs.

A possible sequence of events following unilateral enucleation may be as follows :—

1. A varying degree of damage to the enucleated adrenal gland occurs.

2. The contralateral intact adrenal gland immediately responds to the extra demand put on it ; how this is brought about is still obscure.

3. The enucleated adrenal gland later on responds also, but cannot compete with the more active contralateral adrenal gland.

4. Later on still, a balance is attained in a manner which is obscure. What, for example, inhibits the unlimited hypertrophy of the adrenal glands ?

Host—Homotransplant Relationship.—It was suggested that, in the case of the homotransplanted kidney (Dempster, 1953), mutually interacting processes were at work between the kidney and its temporary host : the kidney reacted against the serum of the host and the latter reacted against the antigenic stimulus of the kidney. The reaction of the homotransplanted kidney took the form of swelling and differentiation of the vascular endothelial cells and the development of immature plasma cells from the local reticulum cells of the kidney. In the present experiments similar features to those taking place in the kidney were observed to be taking place in the attached adrenal and ovary (*Figs.* 677, 678).

The reaction in the adrenal and ovary reflected the strength of the reaction in the kidney. In those instances where the reaction in the kidney was weak or absent, so it was in the adrenal and ovary. The endothelial reaction in the adrenal was never so marked as in the kidney.

Having three organs reacting simultaneously in a similar manner adds significance to the notion that the immature plasma cells, which develop in homotransplanted organs, constitute a genuine reaction of those organs to the serum of the host. Having three organs subjected to the same strength of host antibody, it might be possible to determine (on purely histological grounds which, of course, are not without their limitations) whether each organ succumbs to the alleged antigen-antibody reaction at the same point in time. In the case of the adjacent organs of the kidney which functioned for fifteen days before anuria occurred, there is a suggestion that the ovary was still in a reasonably good functional state at a time when the associated kidney and adrenal had universally disintegrated. It is possible that in certain circumstances homotransplanted endocrine organs may survive for longer periods than other types of tissue. What does appear certain is that provided a homotransplanted organ receives an adequate blood-supply to allow it to function almost normally, that organ will, sooner or later, react against the blood which is, in fact, sustaining its existence.

Halsted's Law and Adrenal Transplantation.—In his original article, Halsted (1909) stipulated that parathyroid tissue auto-implanted in excess of what was urgently required would *not survive*. He made no reference to regeneration and offered no comments on the natural history of auto-implanted tissue.

Survival has a different significance according to whether the tissue is implanted or transplanted. If a fragment of tissue is implanted, the main mass of the fragment immediately undergoes necrosis, leaving only a few peripherally-placed cells alive ; in the rodents, these surviving cells can quickly regenerate and provide the observer with a substantial functioning specimen at the end of thirty days. On the other hand, if the tissue is transplanted, and this now implies a whole organ, survival depends on the adequacy of the immediate blood-flow to that organ. In the former circumstances, if the observer is to find a histological specimen at the end of his experiment, regeneration of the implanted fragment is obligatory ; regeneration, in the case of transplanted organs, is not invariably necessary and of little value so far as the kidney would be concerned. In the kidney, for example, any death of tubular cells will prevent that organ functioning normally—if indeed it functions at all.

The present experiments have demonstrated that Halsted's law has no validity for transplanted endocrine organs. So far as the autotransplanted adrenal is concerned, Levy and Blalock (1939) demonstrated this fact in their experiments, but they made no reference to Halsted's law. The success in autotransplanting organs does not depend on the efficiency of their regenerative powers but on the adequacy of the blood-flow. The kidney requires a rather exact circulation for its normal functioning ; this is not so in the case of the transplanted adrenal. The present experiments have demonstrated that the venous outflow from the adrenal gland can be quite adequate through the capsular veins. Adequate blood-flow is the key factor in all these deliberations.

SUMMARY

1. A technique has been described which allows one to observe the simultaneous behaviour of the auto- and homotransplanted kidney, adrenal, and ovary.

2. An autotransplanted kidney and adrenal can maintain a dog in a healthy state after the removal of the contralateral kidney and adrenal.

3. An autotransplanted adrenal gland suffers parenchymal damage mainly in the zona fasciculata and reticularis. The zona glomerulosa in such circumstances does not give rise to cells which migrate centripetally. There was no indication that glomerulosa cells ultimately develop into cells of the fasciculata and reticularis.

4. Evidence has been presented that the capsule of an autotransplanted adrenal gland is the seat of proliferating islets of glomerulosa cells. It is suggested that such glomerulosa cells arise from

cells in the capsule. These islets show no clear signs of migrating into the zona glomerulosa and no further cellular differentiation occurs.

5. Evidence has been presented which suggests that a homotransplanted adrenal gland and ovary react against their host in a manner similar to that already described for a homotransplanted kidney.

6. It is confirmed that an enucleated rat adrenal gland can regenerate a new cortex from cells in the subcapsular region.

7. It is suggested that homo-implantation is not a valid technique for the study of many of the problems involved in the transfer of tissue from one individual to another.

8. Since an autotransplanted adrenal gland survives in the presence of an intact contralateral adrenal gland, and can maintain life when the latter is removed, Halsted's law is invalid.

Acknowledgements.—The expenses incurred in these experiments were defrayed, in part, by a grant from the British Empire Cancer Campaign. I am indebted to Professor J. M. Yoffey for advice in the preparation of the manuscript. The histological sections were prepared by Mr. J. Griffin and his staff.

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SHORT NOTES OF RARE OR OBSCURE CASES

BILATERAL URIC-ACID CALCULI PRODUCING ANURIA

BY J. O. ROBINSON
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THE occurrence of bilateral uric-acid stones producing anuria must be extremely rare, and for this reason the following case is considered to be worth recording.

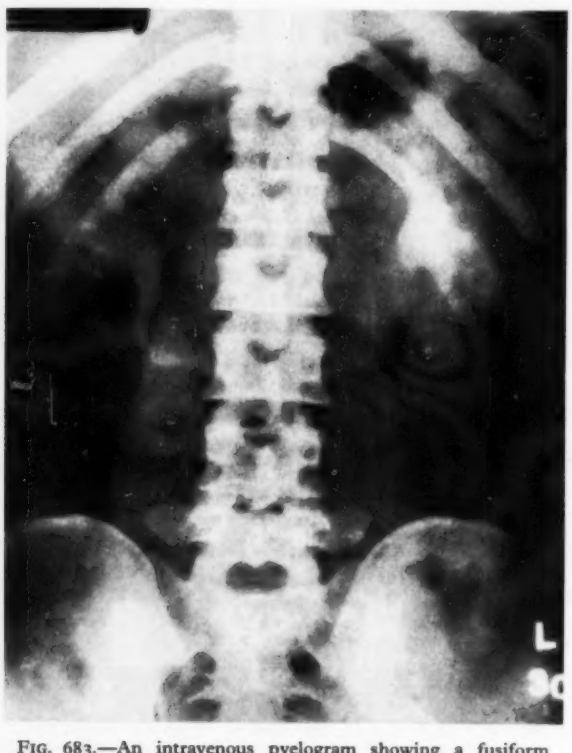

FIG. 683.—An intravenous pyelogram showing a fusiform dilatation of the left pelvis, and a wide superior calix.

CASE REPORT

H. D., male, aged 31 years, a ship's steward. This patient was admitted into a Liverpool hospital on Dec. 20, 1952, complaining that he had not passed water for two days. He gave a nine months' history of a dull aching pain in both loins and in the suprapubic region, which radiated to either side, and became colicky in nature. This was followed by the passage of a blood-stained urine with occasional clots. His diurnal frequency was 2–3 hourly and nocturnal three times. He had always enjoyed good health and denied taking any drugs prior to this attack. On examination he was a well-built man, somewhat obese, with an Eastern facies. There were no abnormal physical signs. B.P. 130/90. His blood-urea was 69 mg. per cent.

FIG. 684.—A further bilateral retrograde pyelogram showing the persistent fusiform dilatation of the left renal pelvis, and two filling defects in the superior calix.

A urethral catheter was introduced into an empty bladder without difficulty, and the bladder was washed out repeatedly without effect. He was placed upon restricted intravenous fluids for a further 24 hours. By the next day, the third of anuria, his blood-urea had risen to 120 mg. per cent. A cystoscope was introduced and catheters were passed up each ureter without difficulty. This resulted in an immediate flow of clear urine, following which his general condition improved rapidly.

Two weeks later an intravenous pyelogram showed a fairly marked pelvic hydronephrosis on the left side, but there was no excretion on the right. A bilateral retrograde

pyelogram demonstrated a filling defect in the left pelvis. The right pelvis and calices were slightly dilated and a moderate degree of pyelovenous backflow occurred.

The patient was anxious to return to London, and was then discharged in good health and passing clear urine. He was referred to St. Bartholomew's Hospital, where he was admitted.

His blood-urea had now fallen to 35 mg. per cent. A further intravenous pyelogram was performed (*Fig.* 683). The plain film showed the kidney outlines to be within normal limits and there were no opaque calculi. The right kidney excreted the contrast medium poorly, but there was no evidence of hydronephrosis. Excretion from the left kidney was better than from the right, but its function remained impaired. The outline of the superior calix was rather broad, though a good concave upper margin persisted. A fusiform dilatation in the region of the pelvi-ureteric junction was noted.

Cystoscopy revealed a normal bladder. A right ureteric catheter became obstructed at 4 cm. The left catheter was passed easily into the renal pelvis. Films (*Fig.* 684) which were taken in the Trendelenburg position showed that there was a filling defect in the left pelvis and that two further small filling defects were present in the region of the upper calix. The right pelvis showed a mild degree of hydronephrosis, but there was no filling defect.

At this stage a diagnosis of bilateral uric-acid stones was considered and was given further support when the blood uric-acid level was found to be 7·4 mg. per cent.

AT OPERATION.—On Feb. 12, 1953, a left pyelolithotomy was performed, when a large guttered stone

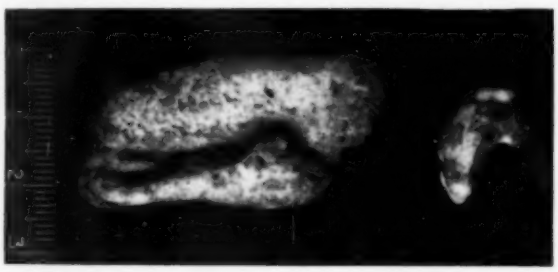

FIG. 685.—A large guttered stone and the smaller stone which was removed from the superior calix. The guttering may be seen in the retrograde pyelogram (*Fig.* 684).

was removed from the pelvis. On sounding the pelvis a further stone was felt in the region of the upper calix; this was subsequently washed out (*Fig.* 685). A ureteric catheter was passed downwards into the bladder without difficulty. Chemical analysis showed that the stones consisted entirely of uric acid.

PROGRESS.—Post operatively there were two days of oliguria, and the blood-urea rose to 65 mg. per cent. He subsequently made an uninterrupted recovery.

The presence of a stone in the right pelvis or ureter was suspected, but had not been demonstrated by any of the intravenous or retrograde pyelograms. On two separate occasions catheters had been passed up the right ureter without difficulty, and only once had an obstruction been felt 4 cm. from the bladder. On Feb. 26 a right ureterogram was performed. An obstruction was again encountered at the lower end of the ureter, but it was possible to pass this and the catheter made to enter the renal pelvis. A series of films were taken, following the injection of Pyelosil, with the catheter placed at varying positions within the ureter. One film (*Fig.* 686) finally demonstrated a filling defect at approximately 4 cm. from the right ureteric orifice. A week later an unsuccessful attempt was made to extract the stone with a 'corkscrew'.

A final intravenous pyelogram, before his discharge from hospital, showed impaired excretion from both sides, with some slight residual hydronephrosis on the left. His blood-urea was 40 mg. per cent.

He was placed on a low purine diet and a potassium citrate mixture. He was seen in the Out-patient Department in July, 1953, and was well apart from a persistent nocturnal frequency of three times. An intravenous pyelogram showed some excretory improvement.

FIG. 686.—A right ureterogram showing the non-opaque calculus at the lower end of the ureter.

He was again seen in October, when his urine contained many uric-acid crystals with an excess of white blood-cells and a small number of red blood-cells. Culture yielded a moderate growth of coagulase-negative staphylococci. Two months later his urine was found to be infected with *Staph. pyogenes* sensitive to terramycin only. His blood uric-acid was 5·7 mg. per cent, hæmoglobin 120 per cent, packed-cell volume 49 c.c. per 100 c.c., red blood-cell count 5,960,000 per c.mm. It was considered possible that the cause of the high blood uric-acid level may have been due to a mild degree of polycythæmia.

DISCUSSION

After careful and prolonged search through the literature no identical case can be found in which bilateral, pure uric-acid calculi produced a complete obstruction to the outflow of urine. There are several references to cases in which a radio-opaque stone was removed from one side, with the subsequent discovery of a non-radio-opaque uric-acid stone on the opposite side. Many cases of a uric-acid calculous anuria have been reported in patients with a congenital absence of one kidney, or who have had a previous nephrectomy performed.

This case illustrates the importance of searching for a second stone on the opposite side, and not accepting the theory that the 'reno-renal reflex' can produce complete anuria, if indeed such a reflex exists. It will be appreciated that considerable difficulty was encountered in demonstrating the stone in the right ureter, and that complete obstruction was only temporary. It is likely that other

similar cases have been found, but that the stone was overlooked and that the ' reno-renal reflex ' was held responsible for the temporary anuria.

The high blood uric-acid in this case demanded full investigation to exclude known causes of a persistently high blood uric-acid level. It will be noted that the blood level has been reduced and maintained at a reasonable figure on a purine-free diet.

SUMMARY

1. A case of anuria due to bilateral uric-acid calculi is reported.

2. The literature has been searched, but a similar case has not been discovered.

3. The importance of looking for a second stone in calculous anuria is stressed.

4. The cause of a high blood-uric level should be investigated in cases with uric acid calculi.

My thanks for permission to publish this case are due to Mr. J. P. Hosford, who performed the pyelolithotomy; to Mr. A. W. Badenoch for his advice; and to Mr. N. K. Harrison for the excellent photographs.

A LARGE LUMBAR HERNIA

By JOHN M. MYNORS, Khartoum

Lumbar herniæ emerge from one of the lumbar triangles, or from wounds and weaknesses in this area.

According to Aird (1950) they may occur in one of two forms :—

1. Following incisions, abscesses, or paralysis.

Fig. 687.—Photograph showing large lumbar hernia on the right side.

2. Spontaneous, through one or other of the lumbar triangles.

In this case the hernia appears to have followed upon a previous abscess the exit of which was the region of the inferior lumbar triangle (of Petit), though the actual hernia was placed rather more anteriorly than usual; it may be that the inflammation had weakened the attachment of the oblique muscles and transversus to the iliac crest, with their subsequent rupture on exertion. It was impossible to discover any source of the past inflammation.

CASE REPORT

A well-built, though mildly obese, Sudanese man of 62 was admitted to hospital on Feb. 15, 1954, complaining of a large swelling over the right iliac crest, which had been present for three years and had first appeared shortly after an incident of a few days' purulent discharge from the same region. No history could be obtained referable to inflammation in any of the organs or structures in the vicinity. The cautery had been applied to the swelling.

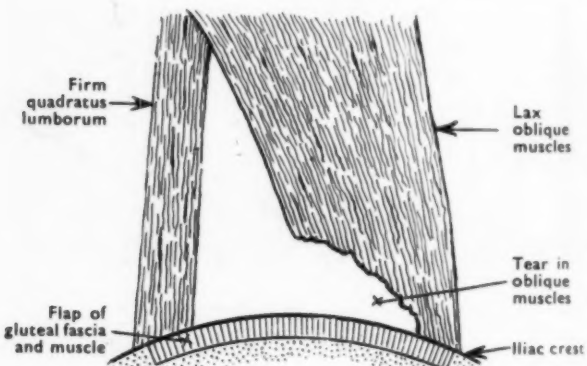

Fig. 688.—Boundaries of the hernia.

On Examination.—There was a soft fully reducible hernia, roughly circular, of 12 in. diameter, coming through an aperture a little anterior to the mid-point of the iliac crest; the aperture readily admitted two fingers (*Fig.* 687).

The only abnormal finding otherwise was a mild dysuria of a few days' duration with some pus cells in the urine; this cleared rapidly following the exhibition of sulphacetamide. In the Sudan such a finding alone is of no significance.

Straight radiographs and intravenous pyelography did not reveal any evidence of past osteomyelitis nor abnormality of the urinary tract. Operative repair was delayed until March 4, 1954, owing to the fact that some of the cautery wounds on the skin were still moist.

At Operation.—The operation was carried out under spinal anæsthesia through a vertical incision and revealed a thin fibrous adherent sac extending downwards and backwards over the gluteal region from an aperture

situated about 4½ in. along the iliac crest from the anterior superior iliac spine. There was no muscle covering to the sac; the latissimus dorsi appeared to have withdrawn medially, and the obliques were torn from the iliac crest for a distance of about 3 in. (*Fig.* 688). There was no evidence of past inflammation and no sinus. It was a sliding hernia containing ascending colon and small bowel; the ascending colon was slack and had as many appendices epiploicæ as in a normal pelvic colon. The sac was excised and the defect closed transversely. After excising fibrous tissue and fascia on the surface of the muscles, the obliques were sutured back to quadratus and down to the flap raised from the gluteal fascia and muscles.

He made an uneventful recovery and was discharged on March 31, 1954, with the wound sound.

DISCUSSION

The hernia may have been either spontaneous or post-inflammatory, especially when one remembers that time matters little to such people and their histories are notoriously unreliable.

It may be that the inflammation was in fact *post hoc* and induced externally by cauterization undertaken for the cure of the lump; nevertheless, he appeared quite definite that the inflammation preceded the swelling, in which case, though there was no evidence of previous internal inflammation, having regard to the contents of the sac and the peculiarity of the ascending colon, it is not impossible that the source of the inflammation could have been a diverticulitis of the colon, though one would have expected some palpable abnormality of the colon even three years later.

SUMMARY

A case of lumbar hernia is described which apparently followed an acute inflammation in the area, and showed rupture of the oblique muscles from the iliac crest for a distance of 3 in.

I wish to thank the Director of Medical Services, Ministry of Health, Sudan Government, for permission to publish; and Mr. P. Kane for the photography.

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A CASE OF ACCESSORY SPLEEN IN THE SCROTUM

BY W. H. W. JAYNE AND A. G. JESSIMAN

WESTMINSTER HOSPITAL

ACCESSORY spleens are commonly seen within the abdomen, but scrotal spleens are a rarity—only 13 cases having been reported to date. We therefore record a further case.

CASE REPORT

A man, aged 44, complained of pain and swelling in the left side of the scrotum.

HISTORY.—At the age of 8 his mother noticed a scrotal swelling and consulted the general practitioner. No treatment was recommended and the swelling persisted. When he was 21 he underwent a medical examination for a job he wished to fill and, on account of the scrotal swelling, was referred to another hospital.

Two operations were performed on the left side of the scrotum. It has been impossible to find out the nature of these operations, but the patient says that the first was followed by a considerable swelling of the left side of the scrotum and that this necessitated a second operation eleven days later. It may be presumed that the first was exploratory and that the second was for the evacuation of a scrotal hæmatoma.

Following these operations the swelling persisted, a little diminished in size, but did not cause any pain. When he attended out-patients on May 19, 1953, there had been aching in the groin associated with a gradual increase in the swelling over the previous fifteen months.

ON EXAMINATION.—General condition excellent. Abdomen—no abnormal physical signs. No inguinal hernia. Scrotum: right side, small spermatocele; left side, large hydrocele associated with a firm mass which could not be differentiated from the body of the testis. Blood-count was normal, and radiography of the chest revealed the presence of a right azygos lobe and a left cervical rib.

AT OPERATION (A. G. J.) (July 7).—A left scrotal incision was made, and on opening the hydrocele the tumour was seen to be covered by the tunica albuginea. As the nature of the tumour was still uncertain, an orchidectomy was performed, the spermatic cord being divided at the external ring. The patient had an uneventful convalescence.

PATHOLOGY.—At the time of the operation the specimen was cut across and the tumour was seen to lie in relation to the upper pole of the body of the testis and quite separate from it. It was red-brown in colour and homogeneous in consistence. A scraping of the surface was taken and incubated on serum-agar (Pulvertaft, 1952; Pulvertaft and Jayne, 1953; Pulvertaft, Wilson, and Jayne, 1953). This revealed the presence of many platelets and a few polymorphs, eosinophils, and lymphocytes, the appearance being similar to scrapings obtained from animal splenic tissue. The diagnosis of splenic tissue was suggested by one of us (W. H. W. J.) and confirmed by the stained sections. (*Figs.* 689–691.)

DISCUSSION

Splenic tissue finds its way into the scrotum as the result of a developmental defect. In early embryonic life the spleen and the left testis are closely related and may even become adherent (Sneath, 1913; Emmett and Dreyfuss, 1943). With the descent of the testis splenic tissue may be dragged down into the scrotum and persist into adult life as an accessory scrotal spleen. A cord is frequently present joining the scrotal and abdominal spleens.

In this case a cord was present extending from the scrotal spleen up to the external inguinal ring, and on post-operative examination of the patient two bands could be felt in the spermatic cord. These were about the size of a normal vas deferens, and one was probably the prolongation of the band found in the specimen.

In 5 cases previously reported (Allbutt and Rolleston, 1908; Sneath, 1913; Heitzman, 1917;

Olken, 1945; Bennet-Jones and Hill, 1952) there was a complete band joining the ectopic to the normal spleen, and in 3 cases found at operation the band was traced to the external or internal inguinal rings (Fischer and Gissel, 1935; Andrews and Etter, 1946; Tate and Goforth, 1949).

FIG. 689.—Low-power view of ductuli efferentes alongside splenic tissue. H. and E. (× 10.)

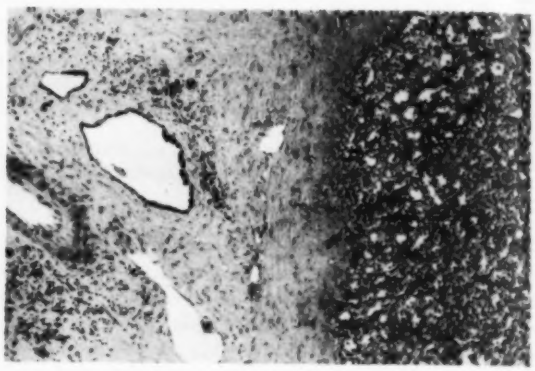

FIG. 690.—Ductuli efferentes alongside splenic tissue. H. and E. (× 30.)

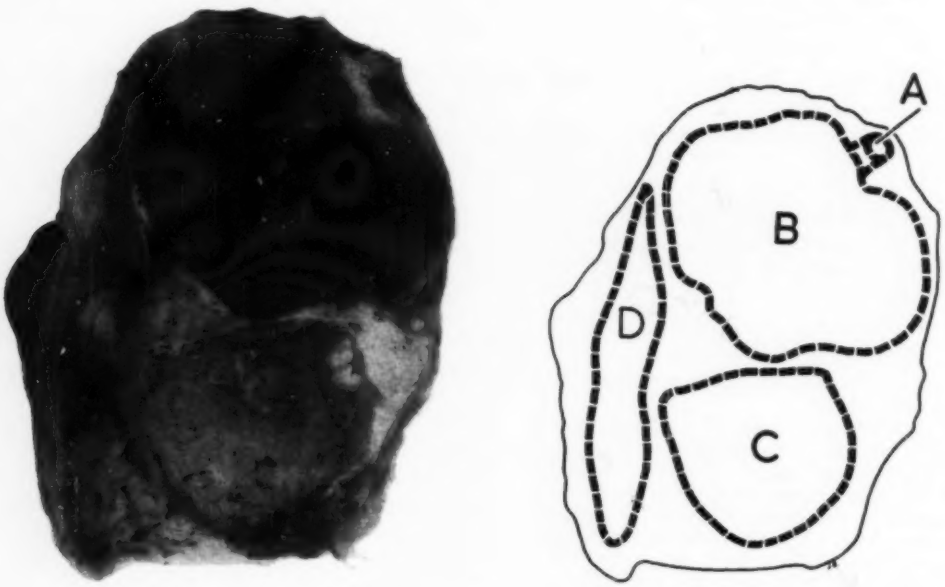

FIG. 691.—Colour photograph of specimen and key. A, Cord; B, Ectopic spleen; C, Testis; D, Hydrocele.

The remainder of the reported cases have been discovered at operation for suspected hernia (Heitzman, 1917; Finaly, 1926), epididymitis (Talmann, 1926; Settle, 1940; Andrews and Etter, 1946), third testicle (Osselladore, 1929), a testicular tumour (Emmett and Dreyfuss, 1943; Tate and Goforth, 1949), or a lymphangioma of the cord (Bennet-Jones and Hill, 1952). In no case has a correct pre-operative diagnosis been made, and in this case the patient was thought to be suffering from a testicular neoplasm.

We wish to thank Sir Stanford Cade for allowing us to report this case; Professor R. J. V. Pulvertaft and Dr. A. D. Morgan for advice in pathology and prints of the photomicrographs; and Dr. P. Hansell for the photograph of the specimen.

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ADULT INTUSSUSCEPTION DUE TO AN ADENOMA OF THE ILEOCÆCAL VALVE

By J. A. HANLEY

It is almost axiomatic that intussusception in the adult has always a local predisposing cause. Polyps and lipomas are the commonest simple tumours initiating this event. The following case illustrates the delayed finding of the precipitating cause. It is also reported as a search of the literature has failed to reveal a similar tumour so situated.

CASE REPORT

The patient, a widow aged 65, was admitted to the North Middlesex Hospital on March 9, 1954. She gave a six weeks' history of colicky central abdominal pain and increasing constipation. For six days previously the pain had been more frequent and severe, and the spasms coincided with the appearance of a lump to the right of the umbilicus. When the colic subsided, the lump tended to disappear. She had been vomiting for three days. The bowels had always been irregular before the present illness. Ten years previously she had had a carcinoma of the epiglottis, proved by biopsy, treated by deep X-ray therapy.

Examination revealed a thin dehydrated woman. The abdomen was distended and visible peristalsis was evident.

Fig. 692.—Barium enema showing filling defect of medial wall of cæcum. Barium would not enter ileum.

A tumour, the size of an orange, was palpable in the right iliac fossa. Rectal examination was normal. A diagnosis of intestinal obstruction, due to carcinoma of the cæcum, was made.

First Operation.—After preliminary rehydration with intravenous saline, laparotomy was undertaken under general anæsthesia. An ileocæcal intussusception was found, which was judged to be present for some time, as evidenced by light adhesions between the constituent parts. It reduced fairly easily. A search was made for any local tumour, but none was palpated, presumably owing to œdema and congestion. To discourage recurrence, the terminal ileum was sutured, side-to-side, to the ascending colon and cæcum. Recovery from the operation was uneventful.

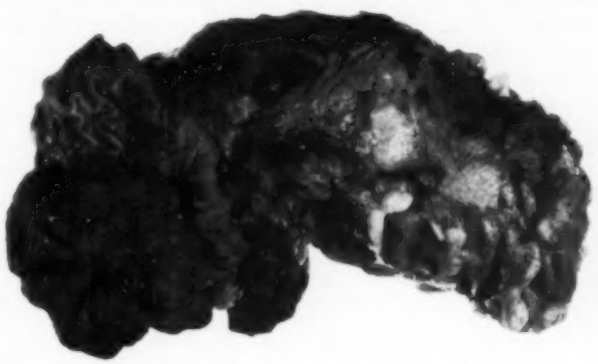

Fig. 693.—Right hemi colon showing polyp. (× ½.)

Progress.—When seen at follow-up on April 9, 1954, she was very well and had no abdominal symptoms. Abdominal and rectal examination were negative for a tumour.

She was seen the next time on July 9, 1954, when she was again asymptomatic. However, there was now a palpable tumour in the right iliac fossa. This was a smooth, soft, mobile, non tender lump about the size of a hen's egg. A provisional diagnosis of a simple tumour of the cæcum was made and a barium enema arranged. This revealed an interesting picture of a filling defect of the medial wall of the cæcum. The barium would not enter the small gut (*Fig.* 692). The rest of the colon was normal. As there was no certainty that the tumour was innocent, and recurrence of the intussusception was likely, another operation was advised. Sigmoidoscopy, to exclude any rectal polypi, was normal.

Second Operation.—Laparotomy was done on Aug. 5, via a right lower paramedian incision. After freeing adhesions, the lump was found on the medial wall of the cæcum. It was felt to be a soft, sessile growth around the ileocæcal valve, as a finger could be invaginated into the cæcum from the ileal surface and the growth was felt to be encircling the finger. The rest of the large and small gut felt normal. The cæcum was opened, via a tænia, as there were some enlarged glands in the adjacent mesentery. The growth was a sessile polyp, about 5 cm. in circumference, surrounding the valve orifice, and it looked simple. The opening in the cæcum was closed and a right hemicolectomy performed, with end-to-side anastomosis of ileum to transverse colon. Recovery was uneventful.

Pathology.—The report by Dr. I. M. Gordon was: "The specimen comprises 3 cm. of terminal ileum, cæcum, and approximately 8 cm. of ascending colon. Surrounding the ileocæcal valve is a large sessile papillomatous growth which is 5 cm. in diameter and appears simple. This is an infected and simple adenomatous polyp." (*Fig.* 693.)

DISCUSSION

A review of some published series of adult intussusception confirms that, in contradistinction to infants, there is practically always a local cause present. Thus, Brown and Michels (1952), of Cleveland, in a series of 15 cases, found only one case to be 'idiopathic', in that a local cause was not present. Teasdale (1953) describes 11 cases of colo-colic intussusception, all due to carcinoma.

The former authors stress that treatment is always surgical, in that the precipitating factor must be eradicated. The alternative treatment of hydrostatic reduction, recognized by them as orthodox for infants, is not, in any case, popular in the British Isles for any age.

SUMMARY

A case of adult intussusception due to a simple tumour of the ileocæcal valve is presented. Stress is laid on the need for a search for a local cause. If this is not obvious at the time of reduction, repeated physical and ancillary examinations must be done to be certain that the intussusception is in fact idiopathic.

Acknowledgements are due to Mr. T. M. Hennebry, under whose care the patient was treated, for permission to publish this case.

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REVIEWS AND NOTICES OF BOOKS

Operative Cholangiographie. Technik, Diagnostik, Praxis. By Priv. Doz. Dr. WALTER HESS, Basel. With a Foreword by Prof. Dr. R. NISSEN, Basel. 10⅛ × 6¾ in. Pp. 201 + xii, with 150 illustrations. 1955. Stuttgart: G. Thieme. DM. 42.

THIS excellent monograph on operative cholangiography deals with a subject which is sadly neglected in this country. The author pays tribute to Mallet-Guy, of Lyons, who was one of the pioneers of this valuable safeguard against post-operative disappointments.

This monograph of 201 pages is excellently produced and profusely illustrated with clear cholangiograms showing the pathological conditions which are likely to be revealed by this method of investigation, including spasm of the sphincter of Oddi with reflux along the pancreatic duct. This work is recommended with every confidence to all surgeons who deal with the surgery of the biliary passages.

Peripheral Nerve Injuries. *Medical Research Council Special Report Series No.* 282. Edited by H. J. SEDDON. 9½ × 6 in. Pp. 452 + xvi, with 276 illustrations. 1954. London: H.M.S.O. 55s.

THE late George Riddoch, who was the secretary of the committee which reported on the nerve injuries of the 1914–18 war, was Chairman of the committee formed to report on these injuries in the more recent war, and had he lived would no doubt have edited the present volume. Professor H. J. Seddon has done so instead, and with the help of a number of collaborators has produced this report consisting of ten chapters in which are discussed such questions as rate of regeneration, nerve-grafts, electromyography, causalgia, injuries of the brachial plexus, the results of nerve suture, and various others. The chapters are written by different contributors whose names appear at the head of each of them, and in this respect the present volume differs from the 1920 one which was a more uniformly written account without individual contributions to its various sections. There is an extensive though incomplete bibliography, but references for some of the statements in the text are not given, e.g., the ill effects of wrapping nerves in amnioplastin, though some details of the effects of this were recorded during the war. It is regrettable that no reference is made to the accurate and well-illustrated account of the regeneration of his own radial nerve reported in great detail by de la Tour Mallett (*J. R. Nav. med. Serv.*, 1946, **32**, 61 and 147).

A great deal of patient research, particularly in histopathology, is recorded in this report and it will be a valuable record for reference. It is a useful supplement to the 1920 issue and adds to our knowledge of these lesions which, except for differences in the types and conditions of the wounds causing them, differ little if at all from those of the previous war.

Surgery of the Adrenal Glands. By WILLIAM WALLACE SCOTT, M.D., Ph.D., Professor of Urology, the Johns Hopkins University School of Medicine; and PERRY B. HUDSON, M.D., Assistant Professor of Urology, Columbia University College of Physicians and Surgeons. 8½ × 5½ in. Pp. 150 + xiv, with 35 illustrations. 1954. Springfield: Charles C. Thomas. 25s.

THIS small monograph deals with the structure, function, and tumours of the adrenal glands. The problem of total bilateral adrenalectomy is not discussed, as the authors consider that insufficient time has elapsed to permit of an accurate evaluation of this operation.

This volume is well written and beautifully illustrated, and as a book of reference it will be useful not only to the surgeon but also to the clinician and pathologist.

British Surgical Practice, Surgical Progress, 1954. Edited by Sir ERNEST ROCK CARLING, LL.D., F.R.C.S., F.R.C.P., F.F.R., Consulting Surgeon, Westminster Hospital; and Sir JAMES PATERSON ROSS, K.C.V.O., M.S., F.R.C.S., Surgeon and Director of Surgical Clinical Unit, St. Batholomew's Hospital; Professor of Surgery, University of London. 9¾ × 6½ in. Pp. 348 + viii, with 125 illustrations. 1954. London: Butterworth & Co. Ltd. 42s.

THIS volume presents an interesting series of articles all showing surgical progress during the year 1954. Rodney Maingot writes on injuries and strictures of the bile-ducts and advocates treatment as soon after the injury as possible.

William Feindel, of McGill, contributes an article on surgical treatment of involuntary movements and describes the operation of 'pedunculotomy', which is performed

to avoid the severe paresis and the occasional occurrence of seizures and aphasia complicating cortical excision.

Bateman and Negus discuss the problem of speech after laryngectomy, while Paul Brand has written a fascinating article on hand reconstruction in leprosy.

Excellent articles on poliomyelitis, blood transfusion, and carcinoma of the stomach are also to be found in this volume.

Sir Stanford Cade has written a very comprehensive article on pelvic viscerectomy for advanced cancer, and this should prove of real value to surgeons who wish to extend their surgical operations for extensive malignant disease of the pelvis.

This volume is a real contribution to British surgery.

Clinical Orthopædics. Edited by ANTHONY F. DEPALMA. Number Four. 10 × 6⅞ in. Pp. 240 + viii, with 162 illustrations. 1955. Philadelphia: J. B. Lippincott Co. 60s.

THIS is the fourth monograph devoted to clinical orthopædics and deals with fractures in the region of joints and with certain dislocations. The value of fixation technique in the treatment of certain fractures is stressed. Two chapters have been devoted to fractures of the patella, and it is interesting to read that total excision of the patella is only used in cases of very severe fragmentation. It is curious to see a chapter devoted to the treatment of recurrent direct inguinal hernia by means of raising an osteoperiosteal flap from the horizontal ramus of the pubis. This form of treatment is not likely to be followed in England.

This volume is not so interesting as the previous three and the case histories are not so instructive; yet, it can be recommended to anyone who is interested in traumatic surgery.

Textbook of Operative Surgery. By ERIC L. FARQUHARSON, M.D., F.R.C.S. (Edin.), F.R.C.S. (Eng.), Surgeon, Royal Infirmary of Edinburgh. 9¾ × 6½ in. Pp. 854 + viii, with 623 illustrations. 1954. Edinburgh: E. & S. Livingstone Ltd. 75s.

THERE is much to be said for a single author text-book of operative surgery and Mr. Farquharson certainly has not disappointed us. In so many of the multiple author books on operative surgery the detail and technique is so comprehensive that the student cannot see the wood for the trees.

This text-book is well written in practical style; the illustrations are well chosen and beautifully reproduced. What more can be said of any text-book? It is bound to be read both at home and abroad, for it combines the best in British surgery.

British Practice in Radiotherapy. Edited by Sir ERNEST ROCK CARLING, LL.D., F.R.C.S., F.R.C.P., F.F.R., Consulting Surgeon, Westminster Hospital, Chairman, International Commission on Radiological Protection; B. W. WINDEYER, M.B., B.S., D.Sc., F.R.C.S., F.R.A.C.S., F.F.R., Professor of Radiology, University of London; and D. W. SMITHERS, M.D., F.R.C.P., F.F.R., Professor of Radiotherapy, University of London. 9 15/16 × 6½ in. Pp. 550 + xii, with 142 illustrations. 1955. London: Butterworth & Co. Ltd. 85s.

THIS is an excellent production, for it presents an interesting and very practical picture of current radiotherapy as practised in Great Britain to-day.

Every aspect of radiotherapy has been adequately covered, and, what is more, by an expert.

No surgeon to-day can afford to be without this book as his constant companion in the treatment of his cancer cases.

The many problems of dosage and measurements, radiobiological damage, radiosensitivity, isotopes, the leukæmias, and ankylosing spondylitis are all discussed in great detail.

Every aspect of cancer as it appears in the human body has been extensively considered and the value of surgery and radiotherapy has been presented in a very practical manner.

The many contributors and the general editors are all to be congratulated on an excellent production of which the medical profession in this country may justly be proud.

Fluid Therapy. By JAMES D. HARDY, M.S. (Chem.), M.D., F.A.C.S., University of Tennessee. 9¼ × 6½ in. Pp. 256, with 77 illustrations. 1954. London: Henry Kimpton. 42s.

THE importance of fluid therapy in the treatment of surgical conditions has only been really recognized during the last decade. To-day every surgeon is fully aware of the great importance of fluid balance, and biochemistry has become part of surgery.

Professor Hardy has given us a comprehensive monograph dealing with every aspect of body fluids and their role in surgical conditions. From a study of body fluid metabolism it is certain that certain endocrine organs have a far-reaching influence on the regulation of body fluid and electrolyte metabolism, and in the future this influence will prove even more important.

In the treatment of burns and in renal failure water balance is recognized as important, but to-day, with extending spheres of operative expansion in every branch of surgery, it is becoming vital to see that body fluid metabolism is properly controlled.

An excellent monograph.

Local Analgesia: Brachial Plexus. By R. R. MACINTOSH, M.A., D.M., F.R.C.S., F.F.A.R.C.S., D.A., Nuffield Professor of Anæsthetics, University of Oxford; and WILLIAM W. MUSHIN, M.A., M.B., B.S. (Lond.), M.R.C.S., F.F.A.R.C.S., D.A., Professor of Anæsthetics Welsh National School of Medicine, University of Wales. Third edition. 7¾ × 4¾ in. Pp. 62, with 32 illustrations. 1954. Edinburgh: E. & S. Livingstone. 10s. 6d.

THE third edition of this excellent book only contains sixty-two pages, but the authors are so precise that the subject of brachial plexus block is fully dealt with from every aspect. Miss McLarty is to be congratulated upon the accuracy and excellence of her numerous illustrations, which materially assist the reader in getting a full knowledge of this useful analgesic technique. This small book is well produced and arranged, and the illustrations are clearly printed. We recommend this book to all anæsthetists, and also to surgeons who may have to use this method single-handed.

Human Limbs and their Substitutes. By PAUL E. KLOPSTEG, Ph.D., Sc.D., Associate Director, National Science Foundation; and PHILIP D. WILSON, M.D., Surgeon-in-chief, Hospital for Special Surgery, New York. 9 × 6 in. Pp. 844 + xiv, with 407 illustrations. 1954. New York: McGraw-Hill Book Company, Inc. 96s.

THIS large and comprehensive volume presents the results of engineering and medical studies of the human extremities and the application of this data to the design and fitting of artificial limbs and to the care and training of amputees. It is, in fact, the combined efforts of some thirty experts—surgeons, engineers, physiologists, psychologists, prosthetists, chemists, and manufacturers, who

are all concerned in producing the best appliances for the unfortunate persons who have lost an arm or a leg.

In this traumatic age when the roads of Britain and America are taking an increasing toll not only of human life but also inflicting grave injuries to the body, especially the limbs, such a book as this is of real value to the orthopædic surgeon.

This book gives an objective survey of prosthetics which is based upon eight years of intensive study sponsored jointly by the Department of Medicine and Surgery, the United States Veterans Administration, and the Surgeon General, Department of the Army. The material has been co-ordinated and edited by the Advisory Committee on Artificial Limbs of the National Research Council.

Every aspect and every facet of the treatment of the amputee has been carefully considered.

This volume will remain the reference book on modern prosthetics.

Surgery of the Elbow. By FREDERICK M. SMITH, M.D., Associate Professor of Clinical Orthopædic Surgery, Columbia University, New York City. Pp. 344, with 270 illustrations. 1955. Oxford: Blackwell Scientific Publications. 77s. 6d.

PERHAPS the real value of this monograph is the pooling of all information concerning the elbow-joint in one volume. This in itself is a great asset to all surgeons who are interested not only in the subject of trauma but also in joint conditions generally. We are living in a traumatic age and more and more fractures, dislocations, strains, and sprains are occurring each year.

This monograph not only deals with traumatic conditions affecting the elbow-joint but also with arthritis, congenital deformities, neoplasms, osteomyelitis, paralyses, loose bodies, and various forms of bursitis. It should become a useful reference volume for all conditions and diseases of the elbow-joint.

Hysterectomy. By JOHN C. BURGH, M.D., and HORACE T. LAVELY, M.D. 10 × 7 in. Pp. 104, with 31 illustrations. 1955. Oxford: Blackwell Scientific Publications. 40s.

THIS monograph deals with the medical and surgical aspects of pelvic disease and gives the indications and contra-indications of hysterectomy in these diseases. The authors, working at the Vanderbilt University of Medicine, have a matured clinical background and a series of over 1000 cases of hysterectomy without a death—no mean record.

In this book the physiological assessment of the disease is compared with a physiological assessment of hysterectomy and of other forms of treatment which might be considered. The technique of abdominal and vaginal hysterectomy is given in detail, and excellent drawings depicting the various stages of the operations are included.

The authors have an excellent common-sense method for the selection of cases for hysterectomy, and if other gynæcologists followed this method there would be fewer disappointments and uniform better results.

A good sound practical monograph which will interest every surgeon who is asked to perform a hysterectomy.

BOOK NOTICES

[*The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.*]

Surgical Technique. By A. V. PARTIPILO, M.D., F.A.C.S., Associate Clinical Professor of Surgery, The Stritch School of Medicine of Loyola University. With a Foreword by ALTON OCHSNER, M.D., F.A.C.S. Fifth edition. 10 × 7 in. Pp. 704, with 548 illustrations. 1953. London: Henry Kimpton. 110s.

X-ray Atlas and Manual of Esophagus, Stomach and Duodenum. By Dr. T. J. J. H. MEUWISSEN, Eindhoven, Holland. With an Introduction by ROBERT D. MORETON, M.D., F.A.C.R., Fort Worth, Texas, U.S.A. 11 × 7½ in. Pp. 687 + xiv, with 1201 illustrations. 1955. Amsterdam: Elsevier (London: Cleaver-Hume Press Ltd.). £8 15s.

Manual of Hand Injuries. By H. MINOR NICHOLS, M.D., University of Oregon Medical School, Portland. With a Foreword by MICHAEL L. MASON, M.D. 8⅞ × 5⅞ in. Pp. 352, with 180 illustrations. 1955. Chicago: Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 72s.

Modern Surgery for Nurses. Edited by F. WILSON HARLON, M.B., B.S. (Durham), F.R.C.S. (Eng.), Consultant Surgeon, S.W. Metropolitan Regional Hospital Board: etc. Third edition. 8½ × 5½ in. Pp. 872 + xxiv, with 419 illustrations. 1954. London: William Heinemann Medical Books Ltd. 27s. 6d.

The Casualty Department. By T. G. LOWDEN, M.A., B.M., B.Ch., F.R.C.S., Consultant Surgeon, Sunderland Royal Infirmary. 9⅝ × 6¾ in. Pp. 278 + viii, with 134 illustrations. 1955. Edinburgh: E. & S. Livingstone Ltd. 37s. 6d.

Transactions of the American College of Cardiology. Vol. III, 1953. 9½ × 6¾ in. Pp. 259. Illustrated. 1954. New York: American College of Cardiology.

Operative Orthopedic Clinics. By LEWIS COZEN, M.D., F.A.C.S., Assistant Professor of Orthopedic Surgery, College of Medical Evangelists, Los Angeles; etc.; and ALVIA BROCKWAY, M.D., Chief of Staff Orthopedic Hospital, Los Angeles. In collaboration with PAUL E. MCMASTER, M.D., F.A.C.S., Clinical Professor of Orthopedic Surgery, University of California, Los Angeles. 10 × 7 in. Pp. 329 + xii, with 310 illustrations. 1955. Philadelphia: J. B. Lippincott Co. (London: Pitman Medical Publishing Co.) 80s.

Neurology. By S. A. KINNIER WILSON, M.A., M.D., D.Sc. (Edin.), F.R.C.P. Second edition. Edited by A. NINIAN BRUCE, F.R.C.P. (Edin.), D.Sc. (Edin.), M.D., F.R.S. (Edin.), Lt.-Col. R.A.M.C., Consulting Physician, Bangour Mental Hospital and St. Andrew's Hospital, Hawick; etc. In three volumes. 9⅛ × 6½ in. Vol. 1, Pp. 702 + index; Vol. 2, Pp. 703–1352 + index; Vol. 3, Pp. 1353–2060 + index. Illustrated. 1955. London: Butterworth & Co. (Publishers) Ltd. £10 10s. Each volume £3 10s.